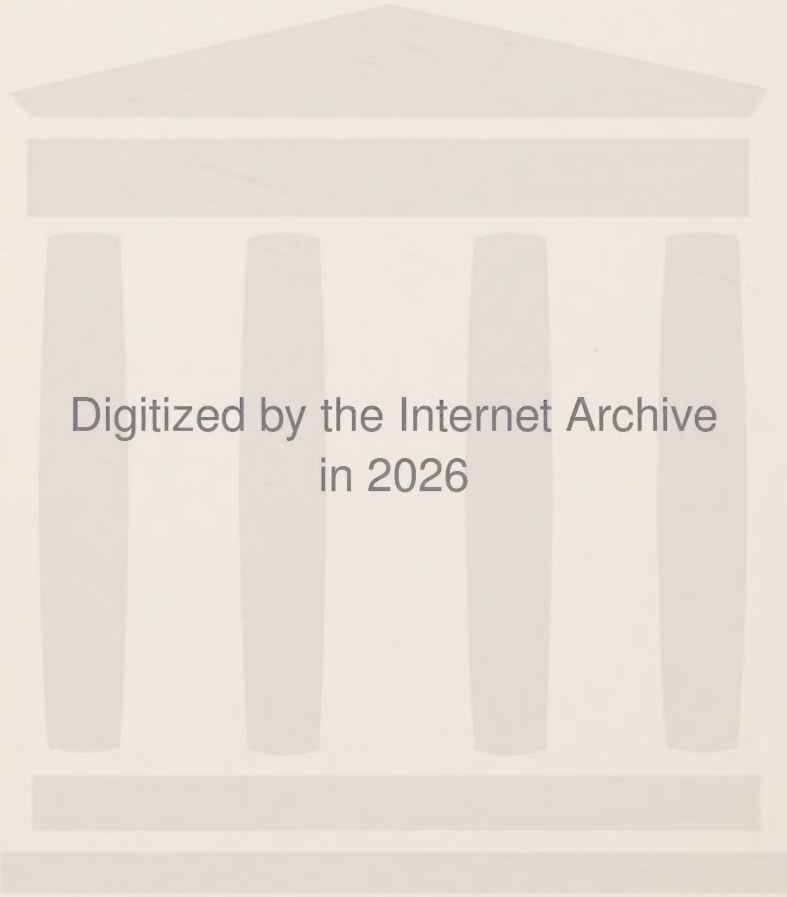


STUDIES ON ALCOHOL RELATED DISABILITIES
IN A MEDICAL INTERVENTION PROGRAMME
IN MIDDLE-AGED MALES

HANS KRISTENSON



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Studies on Alcohol Related Disabilities
in a Medical Intervention Programme in Middle-Aged Males

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av

Hans Kristenson
med lic (Gb)

Malmö 1982



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STUDIES ON ALCOHOL RELATED DISABILITIES

IN A MEDICAL INTERVENTION PROGRAMME IN MIDDLE-AGED MALES

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Malmö 1982

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"To drink healths is to drink sickness"

Thomas Dekker, 1635

This thesis is based on the following papers:

- I. Kristenson H, Trell E, Fex G, Hood B. Serum- γ -glutamyltransferase: Statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. *Prev Med* 1980; 9:108-119.
- II. Kristenson H, Trell E, Hood B. Serum- γ -glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* 1981; 114:862-872.
- III. Kristenson H, Fex G, Trell E. Serum-ferritin, γ -glutamyltransferase and alcohol consumption in healthy middle-aged men. *Drug Alc Depend* 1981; 8:43-50.
- IV. Kristenson H, Trell E. Indicators of alcohol consumption. Comparisons between a questionnaire (Mm-MAST), interviews and serum- γ -glutamyltransferase (GGT) in a health survey of middle-aged males. Accepted by *Br J Addiction*.
- V. Kristenson H, Öhrn J, Hood B. Convictions for drunkenness or drunken driving, sick absenteeism and morbidity in middle-aged males with different levels of serum- γ -glutamyltransferase. Accepted by *Prev Med*.
- VI. Kristenson H, Peterson B, Trell E, Hood B. Hospitalization and alcohol-related morbidity within three years after screening in middle-aged men. Submitted to *J Epidemiol Community Health*.
- VII. Peterson B, Kristenson H, Sternby N H, Trell E, Fex G, Hood B. Alcohol consumption and premature death in middle-aged men. *Br Med J* 1980; 280:1403-1406.
- VIII. Kristenson H, Öhlin H, Hultén-Nosslin M-B, Trell E, Hood B. Identification and intervention of heavy drinking in middle-aged men. Results and follow up 18-72 months. Submitted to *Alcoholism*.

These papers will be referred to in the text by their Roman numerals I-VIII.

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ABBREVIATIONS

GGT	γ -glutamyltransferase synonymous with gamma glutamyl transpeptidase (GGTP) or γ -GT, GT
ASAT	Asparagine aminotransferase
ALAT	Alanine aminotransferase
MCV	Mean corpuscular volume
HDL	High density lipoprotein
MAST	Michigan Alcoholism Screening Test
Mm-MAST	Malmö modification of the brief MAST
ICD	International Classification of Diseases
Sick days	Sickness cash benefit days
ARC	Alcohol related conditions requiring hospitalization
PAIC	Potentially alcohol influenced conditions requiring hospitalization
NARC	Not alcohol related conditions requiring hospitalization
RAD	Individuals registered at the Department of Alcohol Diseases

INTRODUCTION

The Section of Preventive Medicine was opened in October 1974 in the city of Malmö with planned general screening investigations of birth year cohorts. The aim was to attack the major middle-aged cardiovascular risks, including diabetes, starting in 49 year old males. In these comprehensive investigations the enzyme γ -glutamyltransferase (GGT) was included in the laboratory profile.

In February 1975 a pilot study for the detection and evaluation of alcohol related disabilities was initiated. The main idea was to identify heavy drinkers among healthy attendants to the screening investigation and to intervene against their drinking habits and incipient drinking problems on the analogy of the principles of preventive medical treatment for hypertension and hyperlipidaemia. We considered it worthwhile to try to investigate individuals with elevated GGT values and as a psychiatrist I was requested to interview the subjects and examine their drinking habits. At the beginning I had considerable doubts about approaching individuals on the basis of laboratory results but later on GGT proved quite useful as a simple tool in detecting, identifying, treating and controlling heavy drinkers.

The pilot study developed into a research program after about one year with control groups and different birth year cohorts. The primary aims were to test screening and control methods, suitable age for intervention and describe results in individual prevention. Early recognition and treatment of heavy drinking was hypothesized to be beneficial in preventing development to alcoholism. This thesis reports on the design of the study, the first seven years of experience and the results attained.

SCREENING TESTS FOR ALCOHOLISM

1. General principles of population screening as applied to disabilities related to alcohol consumption

In the WHO publication Alcohol Related Disabilities, the screening and methods for early detection as disabilities related to alcohol consumption has been reviewed (1). Certain general principles were taken into consideration, "A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment" (2). Most physicians pay little attention to alcohol as the causal factor in disabilities related to alcohol consumption. Treatment facilities of such disorders should be coordinated with the screening investigation.

A whole-population screening programme should fulfill a series of ten stringent criteria (3). Alcohol related disabilities with certainty fulfill only one of these criteria, i.e. they are indeed an important public health problem. The applicability of the other criteria to alcohol related disabilities is unknown. Understanding of alcoholism remains inadequate, and treatment varies widely from country to country in respect to whom is treated, the methods adopted and the facilities available (4). The 7:th principle, that treatment at a borderline stage of a condition should favourably influence its course and prognosis, is fulfilled e.g. in hypertension. In alcohol dependence the prognosis in general is bad but early detection, clinical investigations and individual support to problem drinkers should reasonably give some measurable positive effects.

The ten criteria are intended to identify subjects for potential clinical treatment. Screening methods may also be used as an epidemiological survey in which the principal purpose is descriptive. Surveys may be useful in increasing public awareness of alcoholism, contributing to the understanding of its causes, helping to differentiate between various syndromes and determining the efficacy of clinical services and of preventive efforts (5).

2. Approaches to screening for alcohol related disabilities

Screening methods for alcohol related disabilities may be directed towards obtaining several different types of information. Heavy drinking, predisposition to abnormally heavy drinking and alcohol dependence may be indicative of increased risk for disabilities related to alcohol consumption. The most common methods of obtaining information are by means of questionnaires or structured interviews. Direct measurements e.g. in the field of physical disabilities, are to be preferred when available. The usefulness of any screening device is restricted by the following factors:

A. Requirement for professional manpower

The time taken in completing direct interview questionnaires about problem drinking varies from less than 25 minutes to 3.5 hours (6, 7). In this study physicians with experience in medical treatment and rehabilitation of alcoholics performed a semistructured psychosocial interview of one hour's duration. Interviews and treatment of the information gained require discretion and responsibility of the staff. The size of the programme was restricted by the requirement for professional manpower for interviews and treatment on an individual basis.

B. Sensitivity, specificity and predictive value

In order to have high sensitivity, a test for a disease must detect nearly all cases with the disease. High specificity is also desirable and attempts to avoid inclusion of healthy subjects in the diseased population. The predictive value of a test indicates the percentage of correct detection of disease in the population studied. In the detection of alcohol related diseases these concepts are difficult to apply because of gradual transitions from normal to abnormal drinking habits, uncertainties in reports of alcohol consumption and in the value of diagnostic tests (8).

C. Reliability

There have been relatively few investigations on the reliability of surveys on problem drinking. In one it was concluded that the frequency of drinking was quite satisfactorily self-reported whereas the actual quantity of alcohol con-

sumed was moderately reliable for non-alcoholics and unreliable for alcoholics (9). In another study the reports of alcohol consumption were valid only when patients had not been drinking (10). Hence the decisive point for the reliability of the investigation of drinking problems is that the individuals must have been sober for some time prior to participation in the investigation.

3. Screening methods in the general population

Screening conducted on the whole population, so called mass screening, is considered of doubtful clinical value. Selective screening offers a more economical use of resources (1, 11). However, "measurement and distribution of drinking patterns and problems in general population studies have an extremely important role to play in our understanding of alcohol problems, precisely because of the difference between the clinical milieu and the outside world" (12). Screening procedures have been carried out on large populations (13-16).

A. Biochemical markers

Measuring the physical consequences of alcohol consumption by means of biochemical tests is now feasible as many laboratory techniques have been developed and the costs for the analyses are relatively low. Hospitalized alcoholics show evidence of hyperlipidaemia and hyperuricaemia and several other laboratory tests, mainly liver enzymes (ASAT, ALAT, GGT), have been reported elevated after moderate and heavy drinking (17-20).

γ -Glutamyltransferase (GGT) is one of the tests which has been most widely used in screening for alcoholism in clinical and population studies (21-26). Correlations between GGT levels and drinking habits have been reported (24-28) although there was also a negative report (29). In Malmö the GGT activity has been determined according to clinical indications since the sixties (30, 31). From the early seventies it has been applied in the treatment of alcoholics (32). The general significance of GGT in clinical use has been critically reviewed by Rosalki (21).

GGT is elevated in about 75 per cent of anicteric patients with liver disorders, even in the absence of clinical evidence of hepatic disease and independent of recent alcohol consumption. In the chronic alcoholic, a heavy alcohol consumption during a short period may show a pronounced acute effect on GGT, but GGT

levels are not acutely elevated after normal social drinking in non-alcoholic subjects who have no previous history of liver damage (21). In male outpatients attending a routine health screening, a correlation between alcohol intake and GGT activity was reported (27). A daily intake of six or more drinks showed increased GGT values in half of the subjects. GGT analyses are also useful for diagnostic confirmation in patients in whom excessive drinking is suspected or known but denied, and serial measurements are valuable for monitoring progress or alleged abstinence from alcohol. When drinking ceases, elevated values revert towards the normal usually within three weeks (21). Thus, it would seem possible to use GGT as a test for measuring physical consequences of drinking in a general population.

Macrocytosis without anemia is one common and consistent abnormality found in alcoholics (33). Mean corpuscular volume (MCV) has been a useful indicator of alcohol consumption in health screening investigations although it is less sensitive than GGT (24, 34). The ratio of plasma amino-n-butyric acid to leucine (A/L) has been reportedly raised in alcoholism (35) but several other studies were unable to confirm these results (36, 37). Serum transferrin and plasma HDL have emerged as markers possibly more specific than GGT (38, 39). These tests as well as linoleic acid in serum lecithin (40) are only available in a few specialized laboratories and are probably not useful for routine determination. Serum ferritin has also been evaluated as an indicator of alcohol consumption in this programme (41).

B. Physical signs

Because of the association of chronic excessive alcohol consumption with physical disease, attempts have been made to use physical signs to identify problem drinkers. In one of the largest of these analyses of some 1 000 000 so called Le Go grids it was shown that the combination of face and tongue signs with tremor was found in 86 per cent of "first degree alcoholics" (42).

The long-term effects of alcohol on the cardiovascular system have been studied (43) in problem drinkers. The prevalence of hypertension was 2.3 times greater among the drinkers than the controls. Hypertension was less prevalent among the previous drinkers than in the groups with known and suspected excessive drinking, suggesting that hypertension is reversible to some extent when drinking is stopped. The conclusion of this study (43) and other recent studies

(44-46) is that blood pressure and pulse rate can be used as indicators of alcohol consumption. These signs can be systematically used in the approach toward individuals with hypertension and heavy drinking (47).

C. "Alcoholism screening tests"

The Michigan Alcoholism Screening Test (MAST), the first and best known such test developed, consists of 25 questions the scoring value of which varies according to their discriminatory power. The MAST correctly assigned 98 per cent of hospitalized alcoholics and only 15 of 526 individuals scored as non-alcoholics on the MAST were revealed as alcoholics by the records search (48). The 10 most discriminating questions were separately evaluated and confirmed that this brief MAST was as effective as the original version (49). A modification of the brief MAST - Mm-MAST has been used in this study (50).

A "Self Administered Alcoholism Screening Test" (SAAST) has also been used in a large population study (51) as well as The Munich Alcoholism Test (MALT) used for the diagnosis of alcoholism (52). Another widely used test, the CAGE questionnaire (53) is easy to administer and consists of only four questions. In a community survey the CAGE was more sensitive than the MAST (54).

DEFINITION OF BASIC CONCEPTS

Since Magnus Huss introduced the word alcoholismus in 1849 (55), there have been many attempts to define the condition (56-61). A new perspective on alcoholism has been introduced (62) and as proposed by WHO (63) there are two distinct concepts: the alcohol dependence syndrome and alcohol related disabilities.

1. The alcohol dependence syndrome

An alcohol dependence syndrome is a recognizable condition which is one of the wider family of drug dependence disorders. The syndrome is multifactorial and exists in degrees. There are no conceptually satisfactory cut-off points that differentiate persons in a normal population from those exhibiting minor alcohol related disabilities and those with the fully developed alcohol dependence syndrome. The most relevant criteria for alcohol dependence are the alcohol withdrawal syndrome and compulsive drinking.

A. The alcohol withdrawal syndrome

The alcohol withdrawal syndrome is a complex of symptoms ranging from a post-intoxication state (hangover) to delirium tremens. The symptoms may include: a) physiological signs (fatigue, headache, thirst, vertigo, gastric disorder, nausea, vomiting, insomnia and fine tremor of the hands); b) psychological symptoms (acute anxiety, guilt or remorse and depression) and c) physical signs (psychomotor and autonomic overactivity, fever, sweating, hypertension, nystagmus, hyperreflexia, seizures and hallucinations).

B. Symptoms of compulsive drinking

Symptoms of compulsive drinking are: a) morning drinking, i.e. drinking the first thing in the morning to steady the nerves; b) blackouts, i.e. memory lapses when drinking; c) loss of control, i.e. craving for more when drinking and d) inability to abstain, i.e. repeated attempts to cut down on drinking have failed.

These definitions are basically in agreement with the National Council on Alcoholism (64).

2. Alcohol related disabilities

An alcohol related disability is considered to be present when there is an impairment in the physical, mental or social functioning of an individual, of such nature that it may be concluded that alcohol is part of the causal nexus determining that disability. Disabilities can exist without dependence, but severe dependence will almost inevitably imply drinking at such a level as to result in a cluster of disabilities (63). Examples of alcohol related disabilities are: a) alcohol related morbidity, b) convictions for drunkenness and drunken driving which illustrates impairment in social functioning and c) definite signs of alcohol related liver disease.

3. Heavy drinking

About 80 g alcohol per day is a hazardous level of consumption and has been used for the classification of heavy drinking in clinical materials (65, 66). A consumption level of 35-60 g alcohol/day appears related to an increased

likelihood for alcohol related morbidity (67). A daily intake of six centilitres of absolute alcohol (i.e. 48 g of alcohol) is enough to induce psychological dependence (68).

In this intervention programme of middle-aged males, the majority of the men have no drinking problems but some have incipient or real drinking problems. Assessment of drinking habits is carried out in a semistructured interview. The alcohol consumption is categorized in non-, light, moderate, heavy and very heavy drinking. Heavy drinking is defined as drinking more than 40 g of alcohol per day. This consumption level is in accordance with recent publications (69-71).

SPECIFIC AIMS OF THE PROJECT

The project was designed to specifically answer the following questions:

1. Is it possible to trace heavy drinkers by means of GGT in healthy middle-aged men?
2. What characterized 46-49 year old men with GGT in the top decentile concerning:
 - a) different biochemical tests and physical measurements?
 - b) answers to a questionnaire?
 - c) drinking habits revealed at interview?
 - d) social parameters including retrospective sick days?
3. Are there any differences between the study population and the participants regarding:
 - a) frequency and number of sick days before the screening investigation?
 - b) hospitalization and alcohol related morbidity within three years after screening?
 - c) premature death within four years follow-up?
 - d) the outcome of these parameters in relation to levels of GGT at screening?
4. What are the effects of the intervention by means of repeated firm counseling and continuous clinical and laboratory follow-up in one random half of the study population?
5. Does intervention cause changing trends in the following:
 - a) drop out frequency?
 - b) levels of GGT?
 - c) sick days per year?
 - d) hospital days?
 - e) mortality?

DESCRIPTION OF POPULATIONS

1. Total population

From October 1974, consecutive middle-aged male birth year cohorts in Malmö have been invited to an intervention programme at the Department of Preventive Medicine, Malmö General Hospital. For this study lists of seven total birth year cohorts were obtained from the population records and invited by letter to the medical screening examination. The material consists of 11 643 males aged 46-49 years. At the invitation all men were living in Malmö and the last screening investigation for this study was performed November 1979. The final attendance rate among the total population after two or three invitations (the third invitation was sent after the total birth year cohort had been investigated, about one year after the first invitation) was 76.1 per cent.

2. Participants

The 8 859 participants were recruited during five years and were assigned to four groups, A, B, C and D according to the various research studies included in the project (Table I). Small differences occurred in size and rate of participation among the different birth year cohorts (Table II).

Table I. Middle-aged males attending screening investigation

Birth years	Numbers	Study groups			
		A	B	C	D
1926 - 1927	2 406	2 046			
1928 - 1929	2 356		4 816		
1930 - 1931	2 137			6 953	
1932 - 1933	1 906				8 859

Table II. TOTAL POPULATION

	1926	1927	1928	1929	1930	1931	1932	1933	1926-1933
Total cohort, n	1593	1555	1604	1461	1459	1361	1320	1290	11643
Number of participants	1252	1208	1223	1133	1118	1019	977	929	8859
Percentage of the total cohort	78.6	77.7	76.2	77.5	76.6	74.9	74.0	72.0	76.1
Number of participants with GGT > 1.40 μ kat/l	120	126	117	116	93	73	78	73	796
Percentage of participants with GGT > 1.40 μ kat/l	9.6	10.4	9.6	10.2	8.2	7.2	8.0	7.9	9.0

3. Non-participants

From the 2 784 members of the total population who did not participate, a small group (n = 200) randomly selected from birth year cohorts 1926-1929 was studied using access to insurance and healthcare records.

4. Study population

To select a study population of suitable size and with high probability of heavy drinking, individuals in the top (tenth) decile of GGT values were selected. This biochemical test was used as a selection criterion because it is objective, easy to obtain and inexpensive. The tenth decile in the 1926 year cohort had a cut-off level of $\text{GGT} > 1.40 \mu\text{kat/l.}^*$ In the following birth year cohorts the same cut-off point was used for practical reasons and thus the study population varies slightly in percentage of the total population (Table II).

Individuals in the study population (n = 796) were invited for a repeated laboratory analysis of the GGT value within three weeks of the primary screening test. This was intended to ensure identification of subjects with consistently elevated GGT (n = 674).

In the 1926 birth year cohort individuals with systemic hypertension, hyperlipidaemia or impaired glucose tolerance were excluded from the material. From the 1927 birth year cohort, only patients with systemic hypertension were excluded i.e. individuals with both hypertension and high GGT values were referred to the hypertension clinic. All other men with high GGT values except some with diabetes mellitus or hypercholesterolaemia were included in the material (n = 585) (Table III).

* The value at that time was $1.65 \mu\text{kat/l}$ which was later changed because of laboratory recalibration to $1.40 \mu\text{kat/l}$.

Table III. Study population. Controls "under treatment" are individuals assigned to the control group who had borderline abnormalities and were excluded.

	n	Percent
Total cohort born 1926-1933	11 643	
Participants	8 859	76.1
Attendants in upper decetile of GGT		
Participants with GGT > 1.40 μ kat/l	796	9.0
Not attending control GGT	53	
Control GGT under cut-off point	69	
Hyperlipidaemia	35	
Hypertension	42	
Diabetes mellitus	12	
Remaining GGT material	585	6.6
Controls "under treatment"	56	
Reduced control group	212	
Controls (total)	268	
Intervention group	317	

A. Intervention group

All individuals with two high GGT values (mean 1.40 μ kat/l) from the 1926 birth year cohort were included in the intervention group. From the following cohorts such individuals were randomly allocated either to the intervention group, or to a control group. The individuals with an even birthdate and uneven birthmonth or uneven birthdate and even birthmonth were assigned to the intervention group. In total there were 317 members of the intervention group.

B. Control group

The other half of the individuals with two consecutive high GGT values were allocated to the control group (n = 268). They had even birthdate and even birthmonth or uneven birthdate and uneven birthmonth. Initially 26 controls were referred to the medical clinic for detailed investigation including liver biopsy. After the investigation they were followed up at the Department of Preventive Medicine. The rest were informed by letter that they had an impaired liver test. They were told in the letter to live as usual, but to be restrictive

with alcoholic beverages, and that they would receive a new invitation to measure their liver enzymes after two years. Understandably, some of the individuals especially those having borderline abnormalities ($n = 56$) in some other test value such as serum triglycerides etc, requested further investigation and treatment, and were then excluded from the control group. The other 212 men received invitations by letter after two, four and six years to repeat the GGT-test at the Department of Preventive Medicine.

5. Comparison groups

The GGT values of the participants were grouped in decentiles and quintiles or arranged in arbitrary consecutive intervals. These groups were used for comparisons between each other and especially with the study population.

A. Ninth decedentile

The ninth decedentile of the GGT distribution roughly represented individuals with GGT values between upper normal laboratory reference value and the top decedentile (GGT 1.08 - 1.40 $\mu\text{kat/l}$). A subsample of these "borderline" males born 1927-1929 was studied as a special control group ($n = 197$). They had originally received information by letter that they had normal laboratory screening tests and were followed up using access to healthcare records.

B. Normal GGT group

To compare the drinking habits in the intervention group with all participants a small group of individuals with GGT values below the tenth decedentile was selected ($n = 62$). These men had slightly elevated blood pressure but were under the cut-off level for hypertensive intervention and attended the Department of Preventive Medicine every year for a blood pressure check up. They were interviewed in the same way as the GGT intervention group.

C. Teetotalers

To facilitate comparisons between different study groups with a certain group of individuals who assumedly did not drink alcoholic beverages, a group of teetotalers was selected. The male members of the Independent Order of Good Templars in Southern Sweden were invited to the screening investigation. Their

mean age was 48.8 years (38-55 years) and 39 men attended the screening programme.

The total population and the different study groups are shown in Figure 1.

TOTAL STUDY POPULATION

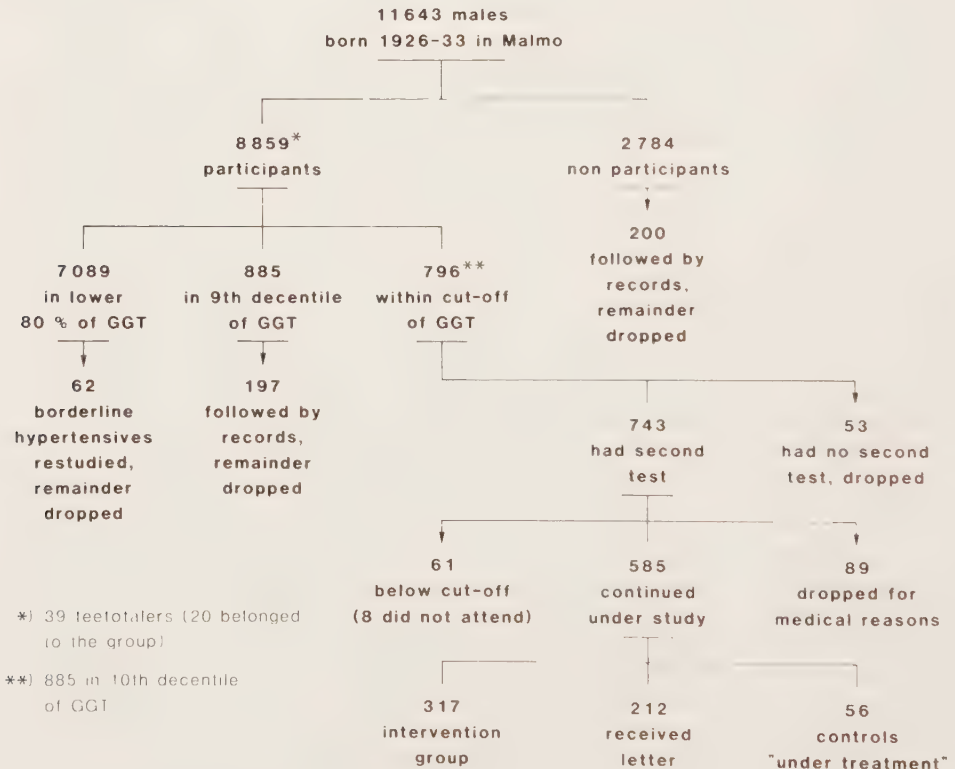


Figure 1. Total study population.

CHARACTERIZATION OF THE STUDY POPULATION

1. Different biochemical tests and physical measurements at screening

A. Distribution of GGT values

GGT was determined in all participants according to standard methods (72). Figure 2 shows the GGT distribution at screening in the males born 1926-1929. The distribution is skewed to the right. The upper decentile of the GGT distribution corresponds to values of $> 1.39 \mu\text{kat/l}$, while the upper normal reference value for GGT at the laboratory is $1.09 \mu\text{kat/l}$ (84.5th percentile).

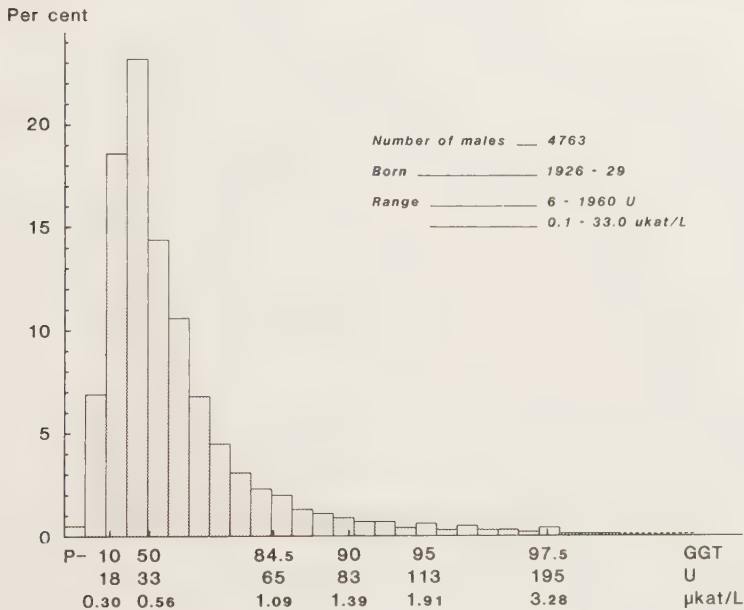


Figure 2. Screening GGT distribution in male birth year cohorts born 1926-29.

The GGT distribution for the participants born 1930-1933 is analogous to that for the 1926-1929 males. As seen in Table IV, however, the GGT values for the 90th and 97.5th percentile were lower in the younger birth year cohorts than in older subjects.

Table IV.

Birth year	Number	GGT μ kat/l in different percentile		
		P50	P90	P97.5
1926-1929	4816	0.56	1.39	3.28
1930-1933	4043	0.56	1.33	2.76

The reasons for these differences in the screening GGT distribution in the two parts of the population might be: a) some of the heavy drinkers in the population did not attend the screening investigation since the intervention programme had probably been widely discussed among these individuals; b) some of the heavy drinkers in the population may have reduced their alcohol consumption when they received the invitation to the screening investigation causing their GGT values at screening to fall below the 90th percentile of the GGT distribution and c) the total alcohol consumption per capita has decreased by about 15 per cent during the last two years in Sweden. This may also be reflected in a reduction of elevated GGT values at screening.

The quintile and decentile limits of the whole screening GGT distribution, males born 1926-1933, are shown in Table V. Comparisons in Paper V-VII are based on these divisions.

Table V. GGT μ kat/l in decentiles (1-10) and quintiles (I-V) for males born 1926-1933. The numerical values are upper limits for each decentile.

Decentile	1	2	3	4	5	6	7	8	9	10
GGT	0.18	0.38	0.49	0.55	0.58	0.66	0.77	0.99	1.39	
Quintile	I		II		III		IV		V	

Normal GGT group

The individuals in this group ($n = 62$) attended the Department of Preventive Medicine once yearly to check their blood pressure. Their GGT values were measured as well. Figure 3 gives the screening GGT values and the GGT values at 1-3 years follow up.

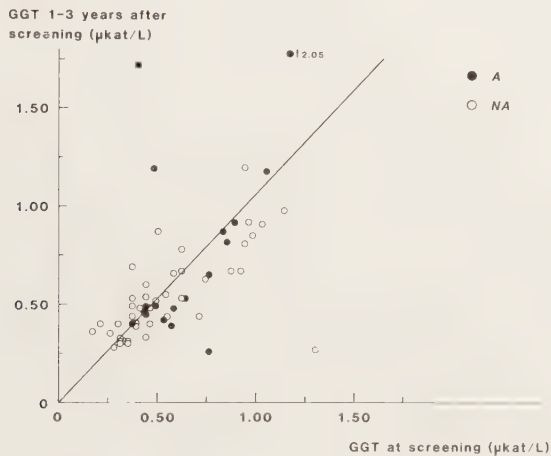


Figure 3. GGT values at screening and at 1-3 years follow-up in the normal GGT group.

As seen in Figure 3 the GGT values were strikingly fixed. The variation in GGT levels was caused by alcohol consumption, or in one case by active rheumatoid arthritis.

B. Serum ferritin (Paper III)

Serum ferritin was analysed in 169 middle-aged men. Ninety-one were heavy drinkers with screening GGT values in the top decile of the GGT distribution. Three men in this group had alcoholic liver cirrhosis. Thirty-nine males were randomized from the same birth year cohorts as the heavy drinkers but with serum GGT activity in the 50th percentile ($0.54 - 0.58 \mu\text{kat/l}$). The remaining thirty-nine were teetotalers, whose GGT was $0.54 \pm 0.35 \mu\text{kat/l}$ (mean $\pm$ SD).

In these subgroups all the individuals, aside from the three cases with liver cirrhosis, were characterized by unremarkable general health screening results. ASAT, ALAT, serum iron and TIBC were analysed in the three groups. Serum iron was significantly higher in the high GGT group where about 50 per cent of the individuals had values above the normal limit. Ferritin concentration was significantly higher in the high GGT group; 67 per cent of the individuals in this group, but only one in each of the two other groups, had values greater than the upper normal limit.

There was no simple relationship between daily alcohol intake and ferritin concentration, nor was there any linear correlation between GGT and ferritin (Figure III:2). The low GGT group and the teetotalers were in general very similar in all other screening tests. All but one of the teetotalers had low serum ferritin values and only one of them had a GGT value greater than 1.4 μ kat/l.

Serum ferritin can thus be utilized as an indicator of alcohol consumption in a population and heavy drinking should be taken into consideration in the interpretation of increased serum ferritin values in individual cases.

C. Body weight, pulse, blood pressure, cholesterol, triglycerides, urate and glucose

The relationships between GGT and body weight, pulse, blood pressure, serum cholesterol, triglycerides, urate and blood glucose at 120 minutes in a glucose tolerance test in the total 1926-1927 screening cohort were studied (Paper I). On the whole, there were highly significant positive correlations between these tests and GGT throughout both the normal and elevated ranges (Table I:7).

The distribution of blood pressure in 3018 participants born 1926-1930 was analysed in two groups (GGT below the median and in the top decile, respectively). The frequency of supine diastolic blood pressure > 105 mm Hg after 10 minutes rest was almost six times higher in the latter group.

Triglycerides were measured in all participants born 1926-1929 with a mean of 1.56 ± 0.89 mmol/l. This value was compared with means for a group of teetotalers, the individuals whose GGT levels were below the median and those in the top decile with confirmed heavy drinking. In these groups the mean triglyceride values were 1.45 ± 0.43 mmol/l, 1.53 ± 0.54 mmol/ and 2.45 ± 1.30 mmol/l,

respectively. The differences between the groups were highly significant ($p < 0.001$). Results of several other tests were compared in the same way and also showed significant differences. Urate was $307 \pm 62^*$ in the total population compared with $294 \pm 59^*$ for the teetotalers, 296 ± 59 in the individuals below the GGT median and $351 \pm 77^*$ in the heavy drinkers (74). Thus a combination of elevated triglycerides and urate values and elevated blood pressure was highly suspect for alcohol overconsumption in otherwise healthy middle-aged males. These results agree well with results of previous studies (44, 73).

2. Answers to a questionnaire

A. Mm-MAST (Paper IV)

A questionnaire consisting of nine questions about drinking habits was used in four different groups of the participants. These study groups were a) normal population, all individuals born 1928 ($n = 1187$); b) normal GGT group ($n = 58$), at interview 41 could be classified as light drinkers or non-users (NA) and 17 (A) were classified as moderate ($n = 7$) or heavy ($n = 10$) alcohol consumers with an alcohol consumption of 52 ± 15 g/day (mean $\pm$ SD); c) heavy drinkers from the intervention group ($n = 125$) with a mean alcohol consumption of 84 ± 44 g/day (mean $\pm$ SD); d) RAD ($n = 223$). Of these 31 were registered after the screening investigation.

The numbers of affirmative answers to Mm-MAST in the study groups are given in Table IV:1.

With a cut-off level of two affirmative answers the diagnostic sensitivity of the questionnaire was 66 per cent in relation to heavy drinking and 73 per cent in relation to alcoholism. The diagnostic specificity calculated from the 41 non-users was 95 per cent (Table IV:2). Of all registered alcoholics (RAD) 90 per cent of the 31 individuals not yet registered were identified. GGT used as an indicator of heavy alcohol consumption in the screening investigation was a poor instrument for the detection of alcoholism assigning correctly only 35 per cent of the RAD group. In combination the two tests identified 82 per cent of the RAD and 97 per cent of the alcoholics who were registered after the screening investigation.

* Urate = $\mu\text{mol} / \text{l}$

B. Medical and social conditions (Paper VIII)

From the 260 questions in the questionnaire, answers to 68 were compared for the intervention and control groups. There were no statistically significant differences in the answers between the groups. The answers, however, are interesting in characterization of the study population. Twenty per cent of the individuals reported previous or present hypertension and nearly nine per cent used antihypertensive medication.

The frequency of affirmative answers to Mn-MAST in the study population was twice that in all the participants. The question "Do you drink a couple of drinks (or beers) a day to relax?" was answered affirmatively about 4 times more often in the study population. Sixty per cent were smokers, and 22 per cent smoked more than 20 cigarettes a day.

Thirty per cent of the subjects were under a doctor's control, 27 per cent had previously been married and 21 per cent had changed employment during the last five years. Of the individuals 18 per cent had had sick leave at least three times in the last year and three per cent had full disability pension. Present or previous back-pain was reported by no fewer than 51 per cent of the men. Fourteen per cent reported a kidney stone attack, while three per cent had had an ulcer operation and only one per cent reported gout.

Nineteen per cent had sought treatment for nervous symptoms and six per cent had been hospitalized for psychiatric disorders. Fourteen per cent had used sleeping pills regularly and about eight per cent used these pills more than three times a week.

3. Clinical investigation (Paper II)

All individuals in the intervention group were examined at an outpatient clinic at the Department of Preventive Medicine. A detailed description of the procedure has been given in Paper II. The individuals in the normal GGT group were interviewed regarding alcohol habits in the same way as the intervention group. The results of the screening most often remained unknown for the interviewer until after the interviews. In addition, to reduce bias, a standardized form was filled in immediately after the interview and given a numerical evaluation. This number was then hidden and could not be changed.

The results from the interviews concerning alcohol consumption in the intervention group (n = 252) and the normal GGT group are shown in Table II:1. In the first group, heavy alcohol consumption was concluded to be present in 54 per cent, moderate alcohol consumption in 22 per cent and light alcohol consumption in 19 per cent. Non-users were 5 per cent. Hazardous drinking levels were concluded to be present in 76 per cent of the intervention group. In the normal GGT group, which presumably reflects the general population of male screening participants in these birth year cohorts, heavy alcohol consumption was reported in 15 per cent, moderate in 25 per cent and light alcohol consumption in 50 per cent; non-users were 10 per cent.

Table II:2 compares symptoms of alcohol dependence in 206 members of the intervention group having alcohol as the certain or probable cause of GGT elevation with the normal GGT group. In the former group symptoms of dependence were frequent while in the latter group such symptoms were exceptional. Thus increased tolerance to alcohol occurred in 59 versus 13 per cent, withdrawal symptoms in 30 versus 2 per cent and morning drinking in 20 versus 2 per cent in the two groups.

4. Social parameters before the screening investigation

A. Marital and occupational status (Paper II)

Statistics on marital status in 1977 for 45-50 year old males were obtained from local census data (75). Comparisons were made between different groups of participants and the non-participants (Table II:4). The most notable difference was an over-representation of divorced individuals in the intervention group and non-participants, in which there was also an increased frequency of unmarried men.

Among men with more than 90 sick days before the screening investigation the differences in marital status were even more pronounced when compared in relation to the GGT levels at screening (Table V:7). The intermediate GGT group was similar to the average Malmö males with 75 per cent of the men married and 25 per cent unmarried or divorced. In the high GGT group, however, there was an over-representation of unmarried or divorced men, accounting for 42 per cent. This is remarkable in comparison with the low GGT group which had an under-representation with only 9 per cent unmarried or divorced males.

The occupational distribution was performed according to a modification of Roe's levels (76). Comparisons were made between the intervention group and various matched subgroups. These include subsamples of individuals in the same birth year cohorts with strictly median screening GGT values and non-participants (Table II:3). There was an under-representation of individuals with disability pension in the median GGT group (0 per cent) and an over-representation in the intervention group (5 per cent). Furthermore, in the intervention group there was a higher frequency of foremen and a lower frequency of unskilled manual laborers in comparison with the other groups. In all groups, however, the frequency of senior clerks and men in managerial positions was practically the same.

B. Convictions for drunkenness, drunken driving and driving under the influence of alcohol (Paper V)

Information was collected from the records of the Inland Revenue Register about all convictions for drunkenness, drunken driving and driving under the influence of alcohol during 1942-1976. A sample of 112 individuals born 1926 and 1927 with screening GGT values in the top decetile was compared with a random sample of 112 participants from the same birth year cohorts with GGT values below the median.

Of the high GGT group 33.0 per cent had been registered with convictions for either drunkenness, drunken driving or driving under the influence of alcohol. For the control group the figure was 11.6 per cent. The ratio was 2.8. In the high GGT group the incidence of convictions for drunkenness and the incidence of drunken driving were 10 and 5 times that in the controls, respectively. Of the individuals in the high GGT group 24 per cent had been sentenced for drunken driving or driving under the influence of alcohol compared with 7 per cent of the controls. The ratio was 3.4 (Table V:4).

C. Accumulative sick days, recent sick absenteeism and diagnoses (Paper V)

Distribution of sick days

From the Insurance Office in Malmö data about sick days were collected for about 25 per cent of the screening participants born between 1926-1929. The total number of sick days per year was registered for a period of 21 years (1955-

1975). With the aim of creating equally large groups of individuals with GGT in various ranges, 1294 individuals were selected for this long-term study. The ranges used were: a) the lowest decedentile (low GGT group), b) at the median, c) above the median, d) between upper normal laboratory value and top decedentile, e) the top decedentile of the distribution (high GGT group).

Of the 290 individuals in the top decedentile, 185 were members of the intervention group. In the intervention group, an evaluation of drinking habits had previously been performed allowing a differentiation into subgroups of individuals with alcoholic (A), probably alcoholic (PA) and non-alcoholic (NA) aetiologies.

For the total period of 21 years there was an accumulation of sick days in the high GGT group of 286 men with 146 720 days compared with the low GGT group of 257 men which had 46 756 days. The disability or sick days per individual in the low GGT group was 182 days (mean) and 84 days (median) compared with 513 days (mean) and 191 days (median) in the high GGT group.

The disability for the individuals with high GGT as well as the group with moderately raised GGT values was compared with the general development of disability for all males in Sweden and also compared with the GGT group below the median (Figure 4). The disabilities for the NA and A subgroups of the intervention group were also compared with the same general population during the 21 years (Figure V:2). As seen in the figures the average male in Sweden in 1963 had a disability of 12 days with a gradual increase to 25 days 1975. In Malmö the disability was 28 days for males aged 45-50 during 1976 (77).

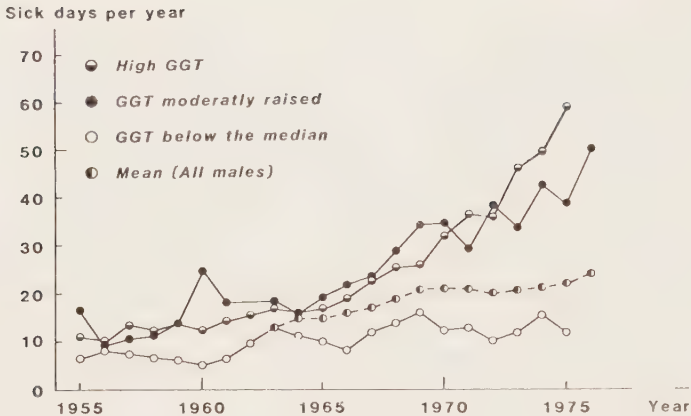


Figure 4

All individuals with 2 high GGT's ($\text{GGT} > 1.40 \mu\text{kat/l}$, $n = 290$), individuals with moderately raised screening GGT's ($n = 67$ mean $1.19 \pm 0.10 \mu\text{kat/l}$, range $1.05 - 1.38$) and individuals with screening GGT below the median for the total distribution ($\leq 0.56 \mu\text{kat/l}$, $n = 100$) during 21 years before screening are compared with Swedish figures for males from the National Social Insurance Board of Sweden (77). Individuals with disability pension are counted as 365 days per year.

The GGT group below the median had "subnormal" sick absence throughout the years with a very limited absolute increase. The group with moderately raised GGT values, the high GGT group and the alcoholic (A) group of the intervention group demonstrated the same general increase during the previous ten years although the degree of disability was different. The A group had a "supernormal" and rapidly increasing disability throughout the 21 years before screening. The NA group had low sick absenteeism with a gradual increase a few years before screening.

The mean and median number of sick days 1955-1975 for the high GGT group compared to those for the low GGT group were 2.8 and 2.2, respectively. The accumulative disability strongly indicates that alcohol consumption is the main cause for the difference in sick absenteeism in these sex and age matched groups. The GGT value at screening correlates positively with the disability during many years before screening. Likewise, half of the individuals below the median of the GGT distribution had fewer sick days than the mean for all Swedish males throughout the 21 years prior to screening (Table V:5).

Recent sick absenteeism

The morbidity in the different GGT groups during three years before screening was analysed. All individuals who had more than 30 sick days per year or more than a total of 90 days for the years 1973-1975 were studied. The frequency of individuals with zero sick days, less than 30 days or more than 90 days is given in Figure V:3. Thirty per cent of the individuals in the low GGT group had no sick absence at all compared with 18 per cent of the individuals in the high GGT group. On the other hand, 14 per cent in the low GGT group had more than 90 days compared with 32 per cent in the high GGT group. The differences in frequency of zero sick days and >90 sick days are statistically significant.

This does not imply, however, that all individuals in the high GGT group had high sick absenteeism. On the contrary no less than 53 per cent of the individuals in the high GGT group had less than 30 sick days during the three years. In the low GGT group this figure was 72 per cent. Thus a GGT value in the top decentile of the GGT distribution indicates a high disability to the group but not necessarily for its single individuals.

Diagnoses in recent morbidity

The distribution of diagnoses among all individuals ($n = 285$) with more than 90 sick days 1973-1975 is given in Table V:9. Of the total 85 528 sick days, musculo-skeletal disorders were the most common category with 32.4 per cent of the days. Mental disorders were second with 19.1 per cent followed by injuries with 12.7 per cent of the total days. Disabilities for the main diagnoses in three different GGT groups were pronouncedly different (Table V:10). The ratios between the high and the low GGT group were highest for injuries with 5.5 and mental disorders with 4.3.

D. Registration at the Department of Alcohol Diseases

The hospital records of the Department of Alcohol Diseases between 1969-1980 were searched. Most registrations at this clinic reflect drinking problems for about ten years. Half of the patients registered are classified as chronic alcoholics.

Of 10 353 men born 1926-1932, 831 or 8 per cent were registered during the twelve year period. There were 449 men (5.7 per cent) registered among the participants and 382 patients (15.8 per cent) among the non-participants. Half of the registered alcoholics from these cohorts (54 per cent) attended the screening investigation. The incidence of new registration at the clinic was calculated in 1975, i.e. before the screening investigation and in 1979 when nearly all participants had been screened. During 1975 and 1979 there were 58 and 32 new cases registered at the clinic from these cohorts. Of these 90 men, 59 participated in the screening.

CHARACTERIZATION OF THE TOTAL POPULATION DURING THREE TO FOUR YEARS FOLLOW-UP

1. Hospitalization and alcohol related morbidity during three years after screening (Paper VI)

Data on all hospital admissions for the years 1975-1979 were used in this study. Of 4571 participants, 963 men or 21 per cent had been admitted to hospital at least once. In a random subsample ($n = 200$ of 1609 non-participants) 54 individuals or 27 per cent had been hospitalized.

Within three years after the screening examination the 963 men had in total 17 158 hospital days, that is 17.8 days per individual or nearly 6 hospital days per individual and year. According to the ICD, mental disorders was the most common diagnostic category with 31.8 per cent of the total hospital days. In this group about half of the days, or 13.6 per cent of the total days, were caused by alcohol psychosis and alcoholism. Neoplasia was the second category with 12.1 per cent of the total days followed by accidents (10.2 per cent) and digestive disorders (9.9 per cent) (Table VI:2).

In the non-participant group 54 individuals had 1737 hospital days for the three years, i.e. nearly 11 days per individual and year. Alcohol psychosis and alcoholism accounted for 28.9 per cent of the total days in this group (Table VI:1).

The frequency of the total 17 158 hospital days within the different GGT quintiles at screening was compared to a theoretical even distribution within the quintiles (Tables VI:3). The observed total days in the highest and lowest quintiles differed significantly. Assuming a probability of 1.0 for an even

distribution, the probabilities of hospitalization were 1.69 and 0.46 in the highest and lowest quintiles, respectively. The probability in the fifth quintile was significantly greater than in all other quintiles ($p < 0.001$).

In addition to classification of morbidity according to ICD, the hospital days were also divided into three new categories. These were: a) illnesses considered to be directly related to excessive drinking, Alcohol Related Conditions (ARC); b) illnesses known to be more common in alcoholics or to be possibly related to excessive drinking, Potentially Alcohol Influenced Conditions (PAIC) and c) all other diagnoses, Non-Alcohol Related Conditions (NARC).

All admissions for the 963 men were analysed and grouped in the new categories. The ARC comprised 127 men, the PAIC 193 and the NARC 643 individuals. These subgroups were also compared according to the screening GGT distribution (Table VI:4).

In the group with NARC, a symmetrical and apparently random distribution was seen among the GGT quintiles. Individuals with PAIC were distributed evenly among the first four quintiles with an over-representation by a factor of 2 in the fifth quintile. This tendency toward increase was most pronounced among men with ARC being 52 per cent in the fifth quintile. A striking difference was seen within the fifth quintile with an increase from 15 per cent (NARC) to 39 per cent (PAIC) and further to 52 per cent (ARC) with an increasing correlation to alcohol in the diagnoses.

Totally 206 men or more than twenty (21.4) per cent of the hospitalized men had serious alcohol problems. In addition many had at least some drinking problems. Thus about 25 per cent of the admitted middle-aged males were heavy drinkers or alcoholics.

2. Deaths during four years follow-up (Paper VII)

Information on deaths occurring after the screening investigation in all males born 1926-1929 was obtained from a register at the Department of Pathology, Malmö General Hospital. All men were 48 or 49 years old at the time of the screening investigation and they were followed for two to four years thereafter (median two years).

The men who died were classified as having an alcohol-positive history if they had a) a history of heavy drinking or b) registration at the Department of Alcohol Diseases (RAD) or c) a GGT value in the top decentile of the GGT distribution with classification (A). All deaths were classified as probably alcohol related, possibly alcohol related or non-alcohol related cases. Of the deceased participants 21/41 or 51 per cent of the deceased males had a history of heavy drinking and 19/41 (46 per cent) had GGT in the top decentile of the GGT distribution. Eleven men were known at the Alcohol Clinic (27 per cent). Altogether 25 men or 61 per cent had a positive history of alcohol. Sixteen of 41 or 39 per cent of the males in this group had alcohol related deaths.

Among the deceased non-participants 13/21 or 62 per cent had a history of heavy drinking and 9/21 (43 per cent) were RAD. A directly alcohol related cause of death was found in 10 of these 21 cases (48 per cent).

The deaths among the participants were concentrated among those whose GGT values were in the upper decentile of the distribution of values among the whole population screened (Table VII:5). The risk of death was six to seven times greater in men with GGT values in the highest quintile than in those with values in the lowest quintile.

TREATMENT

1. Further investigations and referrals

The 317 individuals in the intervention group were further investigated at a special outpatient clinic at the Department of Preventive Medicine. Thirteen subjects (4.1 per cent) did not attend the outpatient clinic and were dropped. The other men had a one hour consultation with a physician. A general physical examination and additional liver tests were performed. A history and a semi-structured interview designed to elicit detailed drinking habits were obtained.

The pertinent findings of the liver tests were summarized in Figure I:2. ALAT, HDL-cholesterol and ASAT were increased in 41, 38 and 34 per cent of the cases, respectively. Measurable serum ethanol was found in fewer than 10 per cent of the subjects.

At the interview a classification of the individuals into three subgroups was performed according to the causes of the GGT elevation. Alcohol was found to be the main factor in 189 cases or 59.6 per cent, called the alcoholic subgroup (A) and the most probable cause in another 52 cases or 16.4 per cent (PA). In the remaining 63 individuals (19.9 per cent), alcohol could be excluded as an aetiological factor (NA).

Twenty one of the 63 subjects in the NA subgroups were referred to the medical clinic for further investigation including liver biopsy. There were seven cases with unclear hepatopathy, one case of biliary cirrhosis, one case of hepatic carcinoma and one with dystrophia myotonica and impaired liver function. Of the remaining eleven men in this group seven had normal findings and four had a slight degree of steatosis at liver biopsy.

Contact was maintained with 241 men in the A and PA subgroups with the aim to reduce their drinking habits.

2. Continuous clinical laboratory follow-up and information

The A and PA subgroups of the intervention group were followed continuously with consultations with the same physician every third month. Laboratory tests (ASAT, ALAT and GGT) were measured every month when the men also had reinforcing contacts with the same nurse. The programme has been described extensively in papers II and VIII. In some cases triglycerides, cholesterol, body weight and blood pressure were also measured. Information on the results of these tests was used in the treatment in the same way as the GGT. Thus the subjects were recommended to lower their alcohol consumption in order to normalize the laboratory and physical test values. Occasionally relatives of the subjects reported that the patients were drinking heavily. These men usually had high GGT levels and were recommended more frequent controls. Generally, no medication was used and the patients were fully able to work. A few subjects reported insomnia or anxiety and were given minor tranquilizers for a few weeks. Individuals who failed to cooperate or after repeated encouragement did not attend consultations were considered dropouts. Three men who appeared intoxicated at the outpatient clinic were referred to the Department of Alcohol Diseases. After more than two years follow-up nineteen men voluntarily discontinued counselling.

3. The aims of controlled drinking and abstinence

One of the purposes in this project was to investigate and evaluate GGT (which correlates positively with alcohol consumption), as a simple tool in the treatment of heavy drinkers. Previous reports with study groups and for short observation periods have suggested that GGT is applicable in control of alcoholics (79, 80).

Treatment aimed at controlled drinking falls into two categories which may be combined in the same programme. One approach uses behaviour therapy techniques, the other involves counselling the alcoholic regarding what appear to be sensible attitudes and usages concerning alcohol (81). The use of a reward (positive reinforcement) for moderation in alcohol consumption is a method that has been applied to outpatients, with the reward for controlled drinking taking the form of continued investment of time and support by the therapists (82).

In this programme elevated GGT values were discussed with the patient as an expression of excessive alcohol consumption. The GGT value was described as a sign of impaired liver function and a warning of impending liver damage. The subjects were individually encouraged to improve their GGT "scores" by changing their drinking habits.

Reports of lowered alcohol consumption were considered reliable only when accompanied by decreases in GGT level. This technique of positive reinforcement was useful in most of the cases. In some patients with severe symptoms of alcohol dependence, however, abstinence was recommended. These men received Antabus from a nurse two to three times weekly for a few weeks and later returned to the usual treatment programme.

This technique of behaviour therapy was developed as a practicable method for support and control of heavy drinking in healthy middle-aged males. Early in the project it became obvious that abstinence was an unrealistic treatment goal for most of these men, although that goal still seems to be the most appropriate for the alcoholics.

EVALUATION AFTER SIX YEARS FOLLOW-UP (Paper II and VIII)

1. Feasibility of the programme

The intervention group was composed of 56 individuals born 1926, comprising the pilot group, and 261 men born 1927-1933, strictly randomized for intervention. Comparisons have been performed between the intervention group and the reduced control group considering the GGT levels in these groups. (Table II:6 and Table VIII:4). There was a significant decrease of the mean GGT value in the intervention group at two and four years follow-up. In the controls there was also a significant decrease in the mean GGT value although the decrease was less pronounced. Although the evaluation and treatment of individuals with elevated GGT values requires a considerable amount of time and professionalism the programme seems feasible and our results indicate that it is possible to treat subjects with high GGT on an individual basis.

2. Overall results of long-term intervention

Of the 241 individuals in the A and PA subgroups 179 (74.3 per cent) remained after two years. The losses within 24 months are given in Table VI. Thirty-six men (15 per cent) dropped out within twelve months.

Table VI. Participation after 24 months in the A and PA subgroups of the intervention group.

	<u>Number</u>	<u>Percent</u>
A and PA subgroups together	241	100
Remaining after 24 months	179	74.3
Losses within 24 months	62	25.7
Referred to other clinics *	10	4.1
Dropouts 0-6 months	19	7.9
Dropouts 7-12 months	17	7.1
Dropouts 13-24 months	16	6.6

* Three of ten men were referred to the alcohol clinic and seven to the medical clinic.

Of the 179 cases still in treatment after two years the overall clinical evaluation from two to five years follow-up was: 82 subjects were improved (34 per cent) 89 unchanged (37 per cent) and 8 individuals had deteriorated (3.3 per cent). Thus 71 per cent of the men in the A and PA groups were improved or unchanged and this outcome was unexpected. Another 19 individuals (7.9 per cent) dropped out after two years treatment. Of these men 4 were improved 14 unchanged and 1 somewhat worse. Thus although the total losses were 30-35 per cent of the intervention group the overall outcome was that about 70 per cent of those men who remained in treatment had not deteriorated in general medical and social adjustment. The dropout frequency for the males in the intervention group in relation to the sick absenteeism four years before the screening is shown in Figure 5.

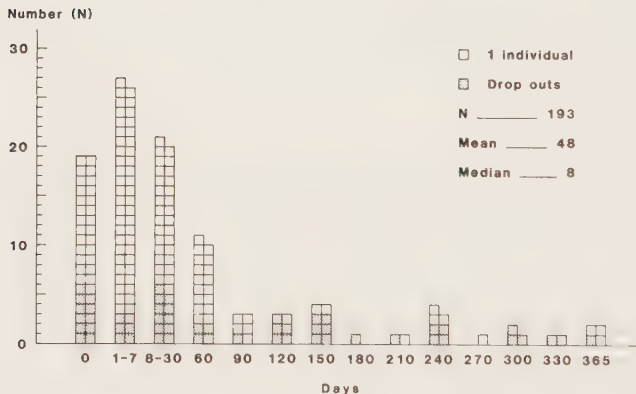


Figure 5

Sick days four years before screening in men born 1927-31 in the intervention group. The dropout frequencies were about 20 per cent in individuals with low sick absence but 80 per cent in individuals with more than 90 sick days.

The dropouts and the mortality for the men born 1926 is summarized in Table VIII:3 and Figure VIII:1. The mortality in the intervention group for men born 1927-1933 ($n = 261$) and the total control group ($n = 269$) is shown in Table VIII:8. There were twice as many deaths in the control group than in the intervention group (10 versus 5). The ratio of probably alcohol related deaths was also 2 (4 versus 2 cases) in these groups.

3. Effect on sick days

The total sick days per year were analysed for the intervention and the reduced control groups during the 21 years prior to the screening investigation. Data were not available for individuals in the birth year cohorts born 1932-1933. The intervention group had an average total of 478 sick days per year during 1955-1975 compared with 437 days for the control group and the difference was not statistically significant ($t = 0.52$). Four years before the screening, however, the mean yearly sick absence was 43 days and 25 days respectively, in the same two groups and thus significantly different ($t = 2.63$). Two years before screening the difference was smaller, being 51 days versus 37 days ($t = 1.57$, n.s.). The mean sick days per year two and four years after entering the screening investigation were compared between the groups. Before the calculations were performed, the individuals who had had more than 50 per cent sick leave during all four years before the screening were excluded. The mean sick absence was then comparable in both groups being 24.0 days per man in the intervention group and 24.7 in the controls (Table VIII:5). During the four years follow-up, the mean sick days per individual and year increased from 24.0 to 29.3 days in the intervention group, or by 5.3 days. In the reduced control group the corresponding figures were: 24.7 to 51.7 days or totally an increase of 27.2 days. The difference between the groups was statistically significant ($p < 0.05$), both at two and four years follow-up. The total difference between the groups after four years treatment was 22 days per individual.

4. Duration of hospital care and alcohol related morbidity

Data on diagnoses and duration of hospital inpatient care were collected and classified for the total study population. In this study all males born 1927-1931 were included and data for the five years after the screening investigation were available. The intervention group contained 195 men in these birth year cohorts and 68 had been hospitalized. The reduced control group consisted of

180 males and 65 of them had been admitted to hospital. In the total controls for these birth year cohorts the respective numbers were 219 and 81.

The reduced control group had 1644 hospital days compared with 808 days for the men in the intervention group. The ratio was 2.2 and when the days were compared. In different diagnostic categories the corresponding ratios were 3.2 in mental disorders, 1.3 in gastrointestinal disorders and 3.0 in accidents or injuries (Table VIII:6). Comparisons between the total control and the intervention groups gave more pronounced differences (Figure VIII:2). Thus the ratio in total hospital days between the groups was 2.4. The ratios in mental disorders, gastrointestinal disorders and accidents or injuries were 4.1, 1.3 and 2.9 respectively.

In order to confirm the influence of alcohol on hospitalization the alcohol related conditions were grouped together. These conditions were alcohol psychosis (291.00-99), alcoholism (303.00-99), liver cirrhosis (571.00-99) and pancreatitis (577.00). In the reduced control group 20 men had 482 days compared with 13 individuals in the intervention group who consumed 133 hospital days. The ratio of total days was 3.9 (Table VIII:7). The corresponding ratio for the total control group compared to the intervention group was 5.0 (Figure VIII:3).

5. Registration at the Department of Alcohol Diseases

Thirty-seven individuals from the intervention and the total control groups had been registered at the Department of Alcohol Diseases before the screening investigation. A record of all individuals who were registered at the Department of Alcohol Diseases within six years after screening was also attained. In the intervention group there were nine new cases compared with ten in the controls. Seven of the nine men in the intervention group had 81 hospital days and 50 of these days were consumed in alcohol related conditions. For the ten controls the corresponding numbers were 546 and 231 days respectively. The ratios between the control and intervention groups were 4.7 and 3.2 in total days and days in alcohol related conditions, respectively.

6. Comparisons between ninth and tenth decedtile of GGT at screening and non-participants

Data on diagnoses and hospital inpatient care were also collected for the individuals in the ninth decedtile group and for the non-participants during three years after screening. Males born 1927-1929 were monitored and compared with the corresponding men in the intervention group. In addition registration at the Department of Alcohol Diseases and records of mortality were penetrated. The results are summarized in Table VII.

Table VII. Comparisons between the ninth decedtile of GGT, the tenth decedtile (intervention group) and the non-participants for males born 1927-1929 in hospitalization, registration at the Department of Alcohol Diseases (RAD) and mortality during three years after screening.

	Ninth decedtile of GGT (n = 197)	Tenth decedtile (intervention group n = 149)	Non-participants (n = 150)
Total days of hospitalization	737	340	1491
Days of hospitali- zation/individual	3.7	2.3	9.9
Days/individual in mental disorders	1.5	0.5	5.3
Days/individual in alcohol related conditions a)	0.07	0.3	3.9
individuals b)	17	21	41
individuals c)	3	3	8

a) alcoholism, alcohol psychosis, liver cirrhosis and pancreatitis

b) RAD during 1969-1980

c) deaths during 1975-1981

The most striking result was the impressive hospitalization among the non-participants.

Furthermore, although the men in the ninth decedtile group had a high degree of hospitalization, i.e. 3.7 total days per individual over the three years of observation, they had only 0.07 days in alcohol related conditions. These figures are compared with 2.3 total days per individual over three years and 0.3 days for alcohol related conditions in the intervention group. Thus the ratio was 4.3 between the intervention and ninth decedtile group in alcohol related conditions. For the non-participants ratios of 56 and 13 were found in comparison to the ninth and tenth decedtile groups, respectively.

DISCUSSION

Screening for alcoholism is at least a two-stage process. In the first step of detection of heavy drinkers and alcoholics the different questionnaires (MAST, CAGE) designed to relate to abnormal drinking behaviour are at present the best instruments (83). In this programme a modification of the brief MAST - Mm-MAST was used to evaluate ordinary drinking habits among the participants. The diagnostic sensitivity of Mm-MAST was 66 per cent in relation to heavy drinking and 73 per cent in relation to alcoholism. These figures are lower than those which have been reported for other questionnaires, but the differences are probably caused by different compositions of the populations studied. The Mm-MAST identified 90 per cent of these individuals who were registered at the alcohol clinic (RAD) after the screening investigation.

Several different biochemical markers have also been used in screening for alcoholism. Research efforts have concentrated on relating laboratory parameters, mainly MCV and GGT, to overall alcohol consumption. When the screening tests are compared against valid consumption data, the sensitivity seems to be around 15 per cent for MCV (83, 84) and 22-44 per cent for GGT, depending on the population investigated (83,84,86). In this project the sensitivity for the GGT was 27 per cent for heavy drinking and 31 per cent for alcoholism. Although GGT is not suitable as a detection instrument for heavy drinkers and alcoholics it was shown that in combination GGT and Mm-MAST identified 82 per cent of the RAD and 97 per cent of the alcoholics who were registered after the screening investigation. Furthermore, the combination of different routine laboratory measurements (such as triglycerides, cholesterol, uric acid, creatinine, ASAT and ALAT) or the combination of laboratory tests, physical signs and affirmative answers to questionnaire (MALT) is probably advantageous compared to a single test such as the GGT (85).

In the second step of identification of drinking problems, however, diagnostic aids and GGT in particular are most useful. Alcohol dependence and abnormal heavy drinking are diagnoses which should preferably not be based on laboratory tests alone, but should also entail a personal evaluation. The use of diagnostic aids is essential because of the vague and undefined symptoms especially frequent in early stages of alcohol overconsumption. Diagnostic aids contribute to a concrete treatment situation when the influence of alcohol on body functions is emphasized and facilitate discussion of the alcohol problem.

For many decades alcoholism has been neglected by physicians and psychiatrists (87). They have been ineffective and disinterested in the treatment of alcoholics. Such a situation is not unexpected since physicians are exposed mainly to the somatic and psychiatric complications of alcoholism and rarely the diagnosis and treatment of the disorder itself (88). Awareness of effective diagnostic aids and successful treatment programmes for early alcoholism could modify attitudes and interest in the problem among physicians. The reliability of assessment of alcohol intake based on personal interviews alone has been low, at least in liver clinics (89). It has earlier been reported that blood-ethanol estimation is a useful and objective adjunct to techniques for investigation of diseases of the liver (90). In the present project the sensitivity of GGT was about 30 per cent for heavy drinking and alcoholism. Even this low figure seems to be relatively good, however, when compared to identification of only 10 per cent of examined alcoholics by general practitioners (96).

One assumption which has frequently been made is that alcoholics and heavy drinkers remain outside the scope of screening programmes (1). This assumption was incorrect in this study as shown by 54-60 per cent participation of individuals RAD from different birth year cohorts. Although morbidity in alcohol related conditions was high in non-participants, the relative improvement seen in the intervention group compared to controls in this aspect demonstrates the presence of significant drinking problems among participants. Another inherent problem in a screening programme is the choice of a suitable lower cut-off level for intervention. In the present study the tenth decedentile was selected for reasons of professional capacity. Comparisons with the ninth decedentile showed slightly greater hospitalization, but insignificant morbidity in alcohol related conditions below the cut-off point. Thus the GGT cut-off point seems to have been appropriate.

The value of a high GGT level as a measure of alcohol related disability was initially uncertain. It could, however, be shown that high GGT values at screening indicated a strikingly high risk for both past and future alcohol related disability. Thus an elevated GGT clearly does not represent a favourable response or defense against alcohol consumption. An unexpected result of the study was that GGT seems to be a predictor for both morbidity and mortality.

One objection to the use of GGT as a screening tool for alcoholism has been its relatively low sensitivity. In this study the sensitivity was 27 per cent,

specificity 95 per cent and predictive value 54 per cent for consumption of >40 g alcohol per day. Among high GGT individuals with lower or no alcohol consumption, hyperlipidaemia, hypertension or liver disease were relatively frequent findings. Thus only about 10 per cent of the tenth GGT decile were considered to be free from disease.

Legal convictions for drunkenness, drunken driving and driving under the influence of alcohol were significantly more frequent in the intervention group than in a random subsample of individuals with GGT values below the median. Furthermore, the retrospective sick days were positively correlated to the GGT levels at screening for as many as 21 years prior to the screening. All the individuals with screening GGT values below the median of the GGT distribution had a remarkably low sick absenteeism during these years compared both with the individuals in the upper decile and with the mean sick absence for all males in Sweden during the same observation time. These results focus attention on alcohol consumption as a major negative contributing factor to social adjustment many years before the physical consequences are measurable and overt. The results are also in agreement with earlier reports which stress the differences in drinking problems in general population surveys compared with clinical populations (12).

Deaths in the participants were concentrated among those whose GGT values were in the upper quintiles of the distribution of values among the whole population screened. A similar correlation did not exist for triglyceride, cholesterol or diastolic blood pressure values which commonly are regarded as risk factors. Screening urate values for the deceased were frequently found in the upper quintiles. Although it is well known that alcoholics have an over-representation of mortality in the 40-50 year age bracket, the high death rate in alcohol related causes (61 per cent) was somewhat surprising. Furthermore, the results illuminate the clinical significance of overconsumption as the risk of dying was six to seven times greater in men with GGT values in the highest quintile than in those with values in the lowest quintile. Hospitalization in alcohol related conditions was seven times greater in men with GGT values in the highest quintile than in those with levels in the lowest quintile, demonstrating the value of GGT as a prospective risk factor.

All these findings in retrospective and prospective morbidity and mortality indicate an urgent need for a public health strategy for the prevention of

alcoholism.

Few studies have been published on the screening and treatment of early stages of alcoholism (79, 80) and the need for long-term controlled population studies using simple and reproducible methods has been indicated (91-93).

The main aim in this report was to investigate the feasibility of intervention in heavy drinking. Of the total population of 11 643 males, 46-49 years old at screening, 8 859 men participated in the screening investigation. Of these men in total 585 or 6.6 per cent of the participants with two consecutive elevated GGT values (mean $>1.40 \mu\text{kat/l}$) in the top decentile of the GGT distribution were followed 2-6 years in either randomly selected intervention or control groups.

The intervention and control groups were well matched at screening with respect to laboratory tests, answers to the questionnaire and registration at the Department of Alcohol Diseases. The mean sick days per year four years prior to screening was higher in the intervention than in the control group.

In the intervention group the treatment consisted of counselling and discussion focused on drinking habits and reduction in alcohol consumption was agreed upon. The GGT level was used to motivate and monitor decreases in alcohol consumption. This bio-feedback technique is similar to the general principles of management, including education, motivation and treatment of patients with hypertension or diabetes mellitus. It is also in agreement with techniques of behaviour therapy using positive reinforcement (81, 82, 94, 95).

Of 241 patients with certain or probable alcohol aetiology for high GGT value in the intervention group, the overall clinical evaluation showed that 34 per cent were improved, 37 per cent unchanged and 3.3 per cent deteriorated. Thus 71 per cent of the A and PA subgroups in the intervention group were improved or unchanged. Another 7.9 per cent dropped out after two years treatment. Thus, although the total losses were 30-35 per cent of the intervention group, the overall outcome was that about 70 per cent of those men who remained in treatment maintained constant or attained better general medical and social adjustment.

The effects of intervention were evaluated five years after the screening and the results were compared with the control group. In the control group the mean yearly sick absence was high before screening and increased by 27 days per individual. This increase illustrates the spontaneous deterioration seen in a group of middle-aged males with high GGT values. The effects of intervention are a marked change in the natural history of this group with an increase of only 5 days sick absence per year after four years. These increases should be viewed with respect to increasing age and previous illness in alcohol related disabilities in both groups.

Hospitalization and alcohol related morbidity were compared for the total control and intervention groups. The ratios of 2.4 in total hospital days, 4.1 in mental disorders and 2.9 in accidents or injuries were found. When considering all alcohol related conditions the ratio was 5.0. Thus intervention resulted in drastic reductions in the need for hospitalization in this age group.

At follow up practically the same number of individuals from both groups had been registered at the Department of Alcohol Diseases but the extent of hospitalization was different. The controls had about four times as many hospital days and twice the mortality as the men in the intervention group.

CONCLUSIONS

Of the total population of 11 643 males, 46-49 years old at screening, 8 859 or 76.1 per cent attended the screening investigation. For these participants a programme was designed to test screening and intervention methods for heavy drinking and to evaluate treatment on an individual basis.

Questionnaires were most suitable for detection of heavy drinking in a general population. Mm-MAST, designed for this purpose, assigned correctly two thirds and three fourths of heavy drinkers and alcoholics, respectively, while GGT detected only one third of heavy drinkers and alcoholics. In combination Mm-MAST and GGT identified 97 per cent of the alcoholics who were registered at the Department of Alcohol Diseases after the screening investigation.

The 46-49 year old men with GGT in the upper decedtile of the GGT distribution were characterized by an ordinary distribution of occupations although there was an increased frequency of disability pensioners and an under-representation of married men. The individuals with high GGT values at screening had an over-representation in sick absenteeism and rapidly increasing disability throughout 21 years before screening. They had high frequencies of affirmative answers to questions indicating an impaired medical and social adjustment. For instance fifty per cent of the men had had back-pain, nineteen per cent had been treated for nervous symptoms and eighteen per cent had had sick leave at least three times during the last year.

In the intervention group there were elevations in the mean weight, recumbent systolic and diastolic blood pressure after ten minutes rest, cholesterol, triglyceride, urate, fasting blood glucose and blood glucose values at 120 minutes in oral glucose tolerance test. Significant differences in mean values were found in comparison with the total group of participants and with teetotalers. Heavy drinking was 3-4 times more frequent in the intervention group compared with the normal GGT group. In the former individuals symptoms of alcohol dependence were frequent while in the latter group such symptoms were exceptional.

There were significant differences between the study population and the total participants regarding retrospective sick absenteeism, hospitalization during three years after screening and in premature death within four years of follow-up. Thus half of the participants with screening values below the median had

an under-representation of sick absence throughout 21 years before screening and a very low absolute increase in the number of sick days, while the study population had a high and rapidly increasing disability during these years.

Individuals with GGT in the highest quintile had a significantly higher risk, compared with those in the lowest quintile, of being hospitalized in alcohol related conditions during three years after screening. Furthermore, the risk of dying was six to seven times higher in the former than the latter group.

After two years treatment 30-35 per cent of the individuals in the intervention group were lost but those individuals who remained in treatment maintained constant or attained better in medical and social adjustment. The intervention caused a significant decrease in the level of GGT at two and four years follow-up. In the controls there was also a significantly lowered GGT level, although to a lesser degree. In the intervention group the mean disability was high before intervention but the increase in sick absenteeism was slight during four years follow-up. In the controls the disability was doubled. Hospitalization and mortality after screening were approximately twice as great in the control group as in the intervention group.

The present results illustrate the possibility of a simple treatment programme to influence heavy drinkers to restrict their drinking habits and possibly to prevent alcoholism. Some of the individuals were totally abstinent for a period and continued drinking in a controlled way while some others could not limit their drinking and were lost. The majority of the men consciously reduced their consumption and adapted to a lower GGT level. The remarkable finding was that, although the men did not cease drinking, the prolonged individual interest and support of a counsellor were sufficient to preserve and maintain health and social adjustment for the majority of the cases. The major prerequisite of such a screening and intervention programme is not the diagnostic aids but rather access to interested and qualified professional manpower.

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Serum γ -Glutamyltransferase: Statistical Distribution in a Middle-Aged Male Population and Evaluation of Alcohol Habits in Individuals with Elevated Levels¹

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Serum γ -glutamyltransferase activity (GGT) was measured in two middle-aged, male Malmö birth-year cohorts. Increased GGT-values were found in 16% of this population sample. There were broad correlations, throughout both the normal and elevated range of GGT values with screening serum triglycerides, 120-min blood glucose in oral glucose tolerance tests, pulse and blood pressure indices, body weight, serum urate and, more weakly, serum cholesterol values. Results of other tests related to liver dysfunction were elevated in only about half of a study group of individuals with elevated screening GGT. Careful evaluation of alcohol habits in this group revealed heavy drinking as the most probable underlying factor in about three-fourths of the cases. We conclude that serum GGT, when included in a general medical screening examination, may help in detecting hidden alcoholism and may also be utilized in an individually oriented program aimed at the prevention of alcoholism.

INTRODUCTION

In previous investigations (7, 18), serum γ -glutamyltransferase (GGT) has been established as a sensitive test of early liver disorders. In clinical studies of alcoholics and heavy drinkers, GGT is elevated in about 70% of the cases (18, 22), and may more sensitively reflect impaired liver status than other commonly assayed enzymes (28). Thus it is suggested that GGT analyses be included in multiphasic health screenings (4, 11). Recently, there have been reports of GGT measurements in population studies (4, 10, 11, 17, 20, 27) where an association between increased GGT levels and heavy drinking was noted. However, there were no detailed descriptions of the evaluation of alcohol habits, and no discussion of possible application of GGT in prevention and control of alcohol abuse.

We included GGT measurements as part of a population investigation which started in October, 1974, at the Department of Preventive Medicine in Malmö. The alcoholic habits of individuals with high GGT values were characterized, and the ability of GGT measurement to assist in instituting an alcoholic treatment and prevention program was evaluated.

In this paper, we report the distribution and various statistical correlations of GGT in our first two middle-aged male birth-year cohorts, born in 1926 and 1927 and the results of the analysis of alcohol habits in individuals with increased GGT values in this sample which is uniform in sex and age.

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BACKGROUND

Malmö is a southern Swedish city of about 250,000 inhabitants, served by one general hospital. A section of preventive medicine was started in the autumn of 1974. Total birth-year cohorts in Malmö are obtained from the population records and invited to the medical screening examination. The final attendance rate after two to three invitations in the 1926–1927 birth-year cohorts was 76.3%.

The screening investigations are performed by nurses and include a medical questionnaire, weight and height measurements, pulmonary function tests, blood pressure and pulse registration, electrocardiogram recording, oral glucose tolerance test, and several other laboratory analyses (hematological data, erythrocyte sedimentation rate, serum sodium, potassium, calcium, phosphate, creatinine and uric acid, plasma triglycerides and cholesterol, high density lipoprotein cholesterol (HDL-cholesterol), serum α_1 -antitrypsin and serum γ -glutamyltransferase (GGT), alanine aminotransferase (ALAT), asparagine aminotransferase (ASAT), and alkaline phosphatase (ALP)).

Abnormal values are checked within 1 to 2 weeks and, if confirmed, lead to an invitation to attend specially designed out-patient clinics within the Department of Preventive Medicine. These include a hypertension clinic, a hyperlipidemia clinic, a diabetes prevention clinic, and, in collaboration with the Department of Alcoholic Diseases, a clinic for diagnosis and treatment of individuals found to have increased GGT values.

MATERIAL

The population basis of the present study comprises all male Malmö residents born in 1926–1927, who were invited to the preventive medical screening examinations mainly in 1974 and 1975 (Table 1). Those with screening GGT values in the upper decile (corresponding to $\geq 1.65 \mu\text{kat/liter}$ in the 1926 birth-year cohort and $\geq 1.45 \mu\text{kat/liter}$ in the 1927 birth-year cohort) were invited for a repeat GGT analysis. Those with elevated GGT levels in the second analysis were allocated either to a group which was invited for further evaluation at the special out-patient clinic described above (study group, S.G.) or, from the end of the 1926 birth-year cohort, to one of two control groups (Table 1). In the 1926 cohort, individuals with systemic hypertension, latent diabetes, or hyperlipidemia were excluded from the S.G. In the 1927 cohort, subjects with hyperlipidemia or latent diabetes were included in the S.G. and only systemic hypertension was given separate priority and these patients were referred to the hypertension clinic (Table 1).

METHODS

(A) Analytical Methods

All screening investigations were performed in the morning after an overnight fast. Venous blood samples were obtained in the supine position after 10 min rest.

Weight and height were measured by routine techniques. A relative weight index according to the formula: actual (measured) weight/ideal weight for body height (A/I weight) (8) was calculated for each individual. The tables of Lindeberg *et al.* (13) were used as ideal weight reference.

Pulse and systolic and diastolic blood pressure were also measured by standard methods at 0 and 10 min rest, both in the standing and the reclining position.

TABLE 1
MALE MALMÖ RESIDENTS INVITED TO PREVENTIVE MEDICAL
SCREENING EXAMINATIONS IN 1974 AND 1975

	1926	1927	1926 + 1927
(a) Total cohort, n^a	1593	1555	3148
(b) Screening participants ^b			
n	1215	1188	2403
Percentage of total cohort	76.3	76.4	76.3
(c) Elevated Screening GGT ^c			
n	195	192	387
Percentage of screening participants	16.1	16.2	16.1
(d) Screening GGT in upper decedentile ^d			
n	120	117	237
Percentage of screening participants	9.9	9.9	9.9
(e) Not attending repeat GGT ^e			
n	15	5	20
Percentage of d (= $\frac{0}{100}$ of b)	12.5	4.3	8.4
(f) Repeat GGT normalized ^f			
n	7	11	18
Percentage of d	5.8	9.4	7.6
(g) Dropouts between repeat GGT and study ^g			
n	3	3	6
Percentage of d	2.5	2.6	2.5
(h) Referred to other clinics ^h			
n	33	5	38
Percentage of d	27.5	4.3	16.0
(i) Controls I (medical clinic) ⁱ			
n	3	22	25
Percentage of d	2.5	18.8	10.6
(j) Controls II (letter information) ^j			
n	3	15	18
Percentage of d	2.5	12.8	7.6
(k) Study group ^k			
n	56	56	112
Percentage of d	46.7	47.9	47.3
Percentage of b	4.6	4.7	4.7

^a Total 1926 and 1927 Malmö male birth-year cohorts.

^b Number of screening participants

^c Subjects with screening GGT $\geq$ upper normal references value (1.33 μ kat/liter in the 1926 birth-year cohort, 1.08 μ kat/liter in the 1927 birth-year cohort).

^d Subjects with screening GGT $\geq$ upper decedentile limit (1.65 μ kat/liter in 1926 birth-year cohort, 1.45 μ kat/liter in 1927 birth-year cohort).

^{e-g} Dropouts.

^h Referred to other clinics (in the 1926 birth-year cohort 19 individuals with hyperlipidemia, 6 hypertension, 3 latent diabetes, 3 overt diabetes, 1 leukemia, 1 chronic hepatitis were referred to other clinics; in the 1927 birth-year cohort priority was altered and only 3 hypertension, 1 overt diabetes, 1 pronounced hypercholesterolemia were referred to other clinics for separate evaluation and treatment.

^{i-j} Control groups (from the end of the 1926 birth-year cohort, 25% of the cases were randomly allocated to the medical clinic, and 25% received letter information).

^k Composition of Study Group after dropouts, and referrals to other clinics and control groups.

GGT AND ALCOHOL CONSUMPTION

In the oral glucose tolerance tests, 30 g glucose/m² BSA in a 10% aqueous solution was ingested within 5 min and (fingertip capillary) blood glucose was determined at 0, 5, 20, 30, 40, 50, 60, 70, 90, and 120 min (in duplicate at 0 and 120 min).

GGT was analyzed by standard methods at the Department of Clinical Chemistry, Malmö General Hospital (24). Due to slight modification during the time of the study, the upper normal laboratory reference value of GGT was somewhat higher at the time of the investigation of the 1926 male birth-year cohort ($<1.33 \mu\text{kat/liter}$) than of the 1927 birth-year cohort ($<1.08 \mu\text{kat/liter}$). All the other laboratory tests referred to here were also performed according to standard technics at the Department of Clinical Chemistry, Malmö General Hospital. Their values are here expressed in SI units.

(B) Evaluation of Alcohol Habits

The individuals allocated to the S.G. were informed by letter of the results of abnormal liver test and requested to return for further assessment. Additional liver function tests were performed and a general physical examination and history were obtained by one doctor (H.K.), a specialist in alcohol medicine. The emphasis at this time was on the liver status but a penetrating interview was included, extending over several visits to evaluate drinking habits.

The investigation of alcohol habits was not concluded until a firm picture of the alcohol consumption pattern and magnitude had been obtained. The intake was then classified in grams of alcohol per day or week on the basis of average consumption of wine, beer, and spirits for the last 3–6 months (22). Table 2 shows the approximate alcohol content of some common beverages, which was used as a guide. The results of these interviews are summarized in Table 3, which also shows the alcohol consumption levels used to classify heavy and moderate drinking (22).

During the interviews symptoms of alcoholism were also evaluated. The criteria specified by the U.S. National Council on Alcoholism (2) were used, such as tolerance, withdrawal symptoms, morning drinking, loss of control, inability to abstain, and blackouts. The results are summarized in Table 4.

Dietary habits, medications, and exposure to organic solvents were analyzed as well. In many cases where alcohol overconsumption could not be documented,

TABLE 2
ESTIMATE OF GRAMS OF ETHANOL IN SOME COMMON ALCOHOLIC BEVERAGES

Beverage	Grams
1 Drink	12
1 Cocktail	18
1 Beer	12
1 Glass of wine	10
1 Pint of beer	20
1 Bottle of wine, 75 cl, 12%	70
Fortified wine, 50 cl, 20%	80
Spirits, 37.5 cl, 40%	120
Whisky, 50 cl	170

TABLE 3
RESULTS OF ALCOHOL CONSUMPTION INTERVIEWS IN STUDY GROUP

	<i>n</i>	%
I Heavy consumption		
(A) 120 g Alcohol/day	22	19.7
(B) 80 g Alcohol/day	17	15.2
(C) 40-60 g Alcohol/day	13	11.6
(D) Regularly ≥ 150 g/week	11	9.8
(E) Irregular bouts ≥ 160 g	13	11.6
Totals	76	67.9
II Moderate consumption 60-80 g at celebrations	9	8.0
III Light consumption	18	16.0
IV Teetotalers	5	4.5
V No information, dropouts	4	3.6

factors like drugs, obesity, and excessive consumption of carbohydrates were found. Table 5 summarizes the factors incriminated as the main cause for the elevated GGT values in the S.G.

The socioeconomic, marital, and occupational status, psychosocial data, and past medical history were obtained from the demographic files and the medical questionnaire included in the screening investigation and, when required, supplemented during the personal interviews. Table 6 shows the occupational composition of the S.G.

(C) Statistical Methods

Calculation of mean values ($\bar{m}$) and standard deviation (SD) were done according to routine statistical methods. Student's *t* test was used for calculating statistical significance.

RESULTS

Figure 1 shows the distribution of screening GGT in the 1926 and 1927 birth-year cohorts. The mean GGT value was higher in the 1926 cohort ($0.92 \mu\text{kat liter}^{-1}$)

TABLE 4
SYMPTOMS OF ALCOHOL ADDICTION IN STUDY GROUP

	<i>n</i>	%
Tolerance	54	48
Withdrawal symptoms	38	34
Morning drinking	29	26
Loss of control	17	15
Inability to abstain	3	2.7
Blackouts	8	7.1
No symptoms	42	38
No information	3	2.7

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TABLE 5
PROBABLE MAIN CAUSES OF ELEVATED GGT IN STUDY GROUP AS CONCLUDED UPON THE
BASIS OF TOTAL SCREENING, QUESTIONNAIRE, AND INTERVIEW DATA

	<i>n</i>	%
Alcohol	81	72.3
Drugs ^a	10	8.9
Dietary factors ^b	16	14.3
Organic liver disease ^c	3	2.7
No information	2	1.8

^a Antiepileptics: 3; antiphlogistics: 2; mixed analgetics (with barbiturates): 5.

^b Overweight > 30%: 4; hyperlipidemia type IV: 3; heavy consumption of carbohydrates: 9.

^c Chronic hepatitis: 2; biliary cirrhosis: 1.

than in the 1927 cohort (0.80 μ kat/liter), which is concomitant with the above-mentioned modification of laboratory reference values.

The GGT distribution was otherwise similar. In the primary screening investigation, 195 men (16.1%) in the 1926 cohort and 192 men (16.2%) in the 1927 cohort had GGT levels higher than the upper normal reference values valid at the time of their investigation (1.33 μ kat/liter and 1.08 μ kat/liter, respectively) (Table 1).

In the S.G., a representative random subsample of individuals with screening GGT in the upper decedtile (Table 1), additional laboratory analyses relating to liver disorders were performed. Figure 2 summarizes the pertinent findings of these tests. ALAT, HDL-cholesterol, and ASAT were increased in 41–34% of the cases, while there was no increased serum bilirubin. Serum lactate dehydrogenase, alkaline phosphatase, plasma IGA, and α_1 -antitrypsin were normal in most individuals. Measurable serum ethanol was found in less than 10% of the cases. Nearly half of the cases in the S.G. had GGT as the only abnormal results of liver test. Symptoms of alcohol addiction were diagnosed almost as often in this group as compared with the group with other laboratory evidence of liver disease.

In Table 7, the relationships between GGT and serum cholesterol, triglycerides, urate, blood glucose at 120 min, body weight, blood pressure, and pulse in the total 1926–1927 screening cohort are represented. On the whole, there were highly significant correlations between these tests and GGT throughout both the normal and elevated range.

TABLE 6
OCCUPATIONAL COMPOSITION OF STUDY GROUP

	<i>n</i>	%
Disability pension	7	6.3
Unskilled manual	12	10.7
Semiskilled manual	19	17.0
Skilled manual	21	18.8
Foreman	18	16.0
Senior clerk	26	23.2
Leading position	9	8.0

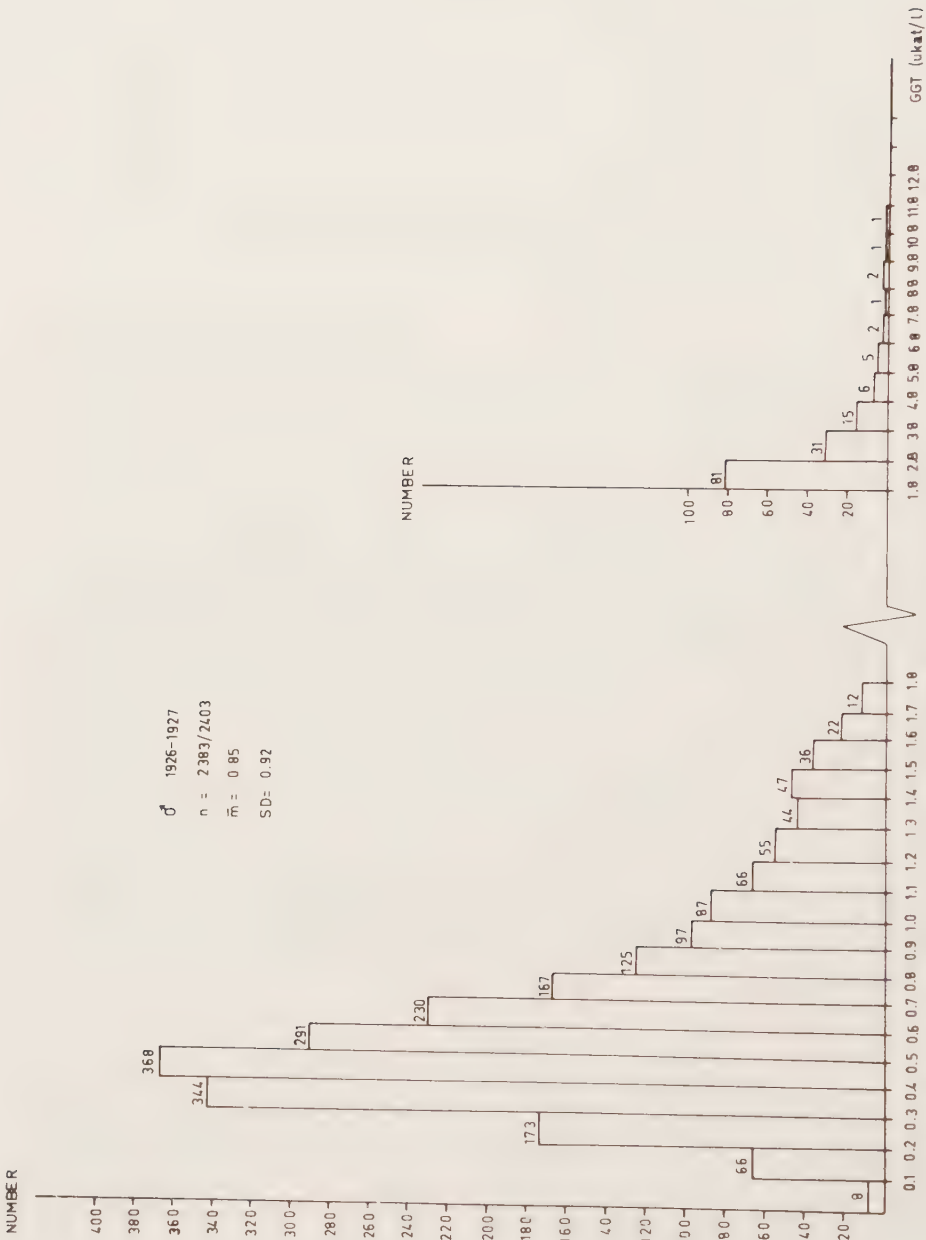


FIG. 1. Screening GGT distribution in 1926 and 1927 birth-year cohorts. The scale is altered at GGT = 1.80 μ kat/liter.

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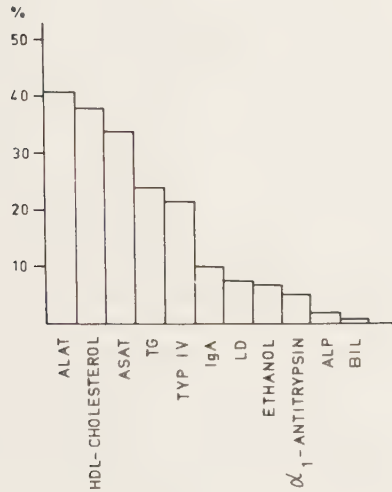


FIG. 2. Frequency of elevated alanine aminotransferase (ALAT), high-density lipoprotein cholesterol (HDL-cholesterol), asparagine aminotransferase (ASAT), triglycerides (TG), hyperlipidemia type IV (TYP IV), plasma immunoglobulin A (IgA), lactate dehydrogenase (LD), ethanol, α_1 -antitrypsin, alkaline phosphatase (ALP), and bilirubin (BIL) values in Study Group.

The results of the alcohol consumption investigations in the S.G. are summarized in Tables 2–6. Heavy alcohol consumption, according to the definitions in Table 3, was established in 68% of the individuals, and moderate consumption in 8%. The remaining 24% consumed less than 8 g of ethanol per week or abstained (Table 3). On the basis of the interviews, the probable reasons for the GGT elevation in the S.G. were established (Table 5). In 72.3% of the cases alcohol was considered the major reason for the GGT elevation, while drugs (antiepileptics, mixed analgesics with barbiturates, antiphlogistics) were incriminated in 8.9% and dietary factors (excessive carbohydrate consumption, overweight, hyperlipidemia) in 14.3%. The mechanisms of the GGT elevation in individual cases are conjectural and under further study, but enzyme induction may possibly be an important factor in many of them. Nonalcoholic organic liver disease (chronic hepatitis, biliary cirrhosis) was found in only 2.7% of the S.G.

A high frequency of alcohol addiction symptoms was found in the S.M. (Table 4). In only 38% were no symptoms documented, while 48% showed tolerance, and 34% had withdrawal symptoms. Even more serious symptoms such as morning drinking (26%), loss of control (15%), and blackouts (7.1%) were prevalent in the group. Such findings are more reminiscent of a group of clinical alcoholics than of a group derived from a preclinical population screening investigation. However, as shown in Table 6, the occupational status of the individuals in the S.G. supports the fact that it is composed of sociomedically intact, apparently healthy individuals.

DISCUSSION

There are earlier reports of GGT measurements in population studies (4, 10, 17, 20, 27). However, these samples are insufficiently defined in relation to their

TABLE 7
RELATIONSHIPS BETWEEN GGT AND SERUM CHOLESTEROL, TRIGLYCERIDES, URATE, BLOOD
GLUCOSE, BODY WEIGHT, BLOOD PRESSURE, AND PULSE IN THE
TOTAL 1926-1927 SCREENING COHORT^a

GGT <i>n</i> ^b	0.01-0.36 (334)-416			0.37-0.72 (897)-1118		0.73-1.08 (343)-435		1.09-1.44 (147)-182	
	<i>m</i>	SD	<i>P</i> ^c	<i>m</i>	SD	<i>m</i>	SD	<i>m</i>	SD
Triglyceride	1.14	0.44	<0.0005	1.31	0.62	1.64	0.96	1.77	0.97
Cholesterol	5.60	0.95	<0.0005	5.87	1.00	6.04	1.07	6.13	1.11
Urate	285	60.0	<0.0005	302	59.3	322	63.5	327	60.2
Glucose (min)									
0	4.32	0.66	<0.0025	4.43	0.96	4.51	0.94	4.61	0.82
120	4.88	1.38	<0.0005	5.11	1.41	5.52	1.65	5.39	1.83
A/IW	1.05	0.13	<0.0005	1.07	0.14	1.13	0.16	1.16	0.16
Pulse (min)									
0	73.1	10.7	<0.15	72.8	11.7	73.5	11.6	75.3	12.5
10	69.6	9.48	<0.15	69.2	10.4	70.4	10.8	71.4	11.6
BPS (min)									
0	134	16.0	<0.0005	136	17.0	140	17.8	143	19.2
10	126	14.8	<0.0005	128	15.2	133	17.1	135	17.9
BPD (min)									
0	86.3	10.8	<0.0005	88.4	10.2	92.2	11.1	94.4	12.3
10	84.0	10.1	<0.0005	86.0	9.86	89.9	10.8	91.4	11.1

epidemiological substrata. Our material is age- and sex-uniform and as complete as may be achieved in a voluntary population investigation. Of the total 1926-1927 birth-year cohorts in Malmö, 76.3% participated in the screening. It may be assumed that generally they exhibited a better socioeconomic and health status than the 23.7% who did not respond to the invitations (25). However, even in our largely nonsymptomatic population sample, screening GGT levels exceeding upper normal reference values were found in 16%. The S.G. is composed of individuals with screening GGT in the upper decentile and in our opinion is representative, even though there were small losses because of nonattendance or referral to other clinics or control groups (Table 1).

The assessment of alcohol habits is notoriously difficult in individuals with alcohol problems. This, and associations between GGT and other investigative variables, renders the evaluation of the relation between GGT and alcohol consumption highly intricate. Nevertheless, the present study seems to indicate that careful interviewing in apparently healthy individuals with elevated GGT values reveals heavy drinking as the most important underlying factor in the large majority of cases.

It may be argued that an increased GGT value created a presupposition of alcohol overconsumption that was more or less automatically confirmed by repetitious directed questioning. Completely double-blind and objective conditions are hard to achieve and were not a primary goal of our study. It is our belief that the alcohol consumption findings in our study are if anything too low because of previously mentioned tendencies to deny alcohol habits.

The predictive value with respect to heavy drinking of two consecutive GGT values in the upper decentile of the GGT distribution was 72.3% (Table 3). Twenty

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TABLE 7—Continued

GGT <i>n</i> ^b	1.45–2.16 (109)–143		2.17–3.60 (61)–83		≥3.61 (31)–42		<i>P</i>	Total (1922)–2419	
	$\bar{m}$	SD	$\bar{m}$	SD	$\bar{m}$	SD		$\bar{m}$	SD
Triglyceride	1.80	1.23	2.01	1.26	2.79	2.26	<0.0005	1.45	0.87
Cholesterol	6.09	0.96	6.38	1.04	6.30	1.22	0.01	5.91	1.03
Urate	335	73.7	340	73.0	363	96.4	<0.0005	309	64.9
Glucose (min)									
0	4.74	1.81	4.83	1.10	5.15	2.20	<0.0005	4.48	1.02
120	5.84	2.14	5.92	2.06	6.77	2.40	<0.0005	5.26	1.61
A/TW	1.11	0.16	1.15	0.16	1.16	0.16	0.0025	1.09	0.14
Pulse (min)									
0	78.4	13.3	75.2	12.4	81.4	13.0	<0.0005	73.7	11.8
10	73.9	12.3	71.7	11.3	76.9	10.2	<0.0005	70.1	10.7
BPS (min)									
0	142	20.1	145	20.5	149	16.7	<0.0005	138	17.8
10	134	17.4	137	19.3	141	16.9	<0.0005	130	16.4
BPD (min)									
0	91.8	11.8	94.2	11.2	96.2	11.2	<0.0005	89.7	11.1
10	89.6	11.3	90.9	10.2	94.9	11.1	<0.0005	87.3	10.6

^a Mean values ($\bar{m}$) and standard deviation (SD) in 1926 and 1927 birth-year cohort of screening serum triglycerides (mmole/liter), cholesterol (mmole/liter), urate (μ mole/liter), fasting blood glucose (mmole/liter), blood glucose at 120 min in oral glucose tolerance test (mmole/liter), relative body weight (index), recumbent pulse at 0 min (beats/min), recumbent pulse after 10 min rest, recumbent systolic blood pressure at 0 min (BPS 0; mm Hg), recumbent systolic blood pressure after 10 min rest (BPS 10), recumbent diastolic blood pressure at 0 min (BPS 0), and recumbent diastolic blood pressure after 10 min rest (BPD 10) in consecutive γ -glutamyltransferase (GGT; μ kat/liter) levels.

^b *n*, Number of individuals. Numbers within parentheses are numbers of glucose tolerance tests (glucose 120).

^c The *P* values express the significance levels of the difference between the values in the lowest GGT group (0.01–0.36 μ kat/liter) and the total cohort on the one hand; and the highest GGT group (>3.61 μ kat/liter) and the total cohort on the other hand.

individuals with increased screening GGT did not attend a repeat examination (Table 1). Of the 217 remaining, only 18 had lowered GGT below the cut-off point, and we know that these individuals include heavy drinkers. This clearly indicates that a single GGT determination is of the same predictive value as two consecutive measurements, and that very little is gained by rechecking elevated screening GGT values. From the present data it is not possible to calculate the sensitivity or the specificity of GGT. Investigations aimed at determinations of sensitivity, specificity, and efficiency of GGT in relation to alcohol abuse are currently under way.

GGT was the only abnormal liver test in about half of the S.G. This suggests that GGT offers one of the most sensitive tests of early hepatic disturbance (7, 18, 19, 27, 28). In the majority of the cases alcohol was considered the main reason for the GGT elevation (Table 5). There are, however, other factors which may influence GGT levels. Age and sex are of importance (4, 20, 28), but were kept con-

stant. Drugs, in particular antiepileptics and barbiturates (7, 18), were a possible cause in 10 cases (Table 5). Dietary habits, with carbohydrate overconsumption (7, 14) and/or obesity (4, 20) may have been of importance in 16 cases, while nonalcoholic organic liver disease was astonishingly infrequent, being found in only three cases. A combination of the above-mentioned factors and alcohol may be present in some cases, especially those with drug ingestion. It is obvious that the relationships between GGT and alcohol consumption are not obligate or simple, and that an increased GGT value must be professionally evaluated in each individual. This is supported by the significant associations between GGT and a number of test variables in the whole screening population (Table 7). There were very strong correlations, both throughout the normal as well as the elevated range of GGT with serum triglycerides (14), cholesterol, urate (27), 120 min blood glucose (15), body weight (4, 20, 28), blood pressure (1, 3, 9, 16), and pulse. We are presently investigating the biochemical mechanisms of these relationships.

It is noteworthy that the S.G. was not composed of overtly alcoholic or otherwise diseased individuals. Only 7 (6.3%) had disability pensions and the majority were of the middle or upper middle class (Table 6). But further investigation revealed clinical symptoms of alcohol addiction in more than 60% of the S.G., including cases with no other abnormal liver tests than GGT (Table 4). We think that this justifies a preventive trial (5, 6). Accordingly, the application of GGT measurements in population screening may serve not only to identify individuals with occult alcoholism, but may also offer a starting point for individually oriented preventive measures.

We have followed our study group continuously since 1974–1975. Our preliminary conclusion is that GGT is a useful instrument in the prevention of alcoholism in individuals. The abnormal value acts as an initial stimulus and repeated measurements give continuous feedback in the elimination or reduction of alcohol abuse (12).

However, the subject of GGT in population studies and in prevention of alcoholism needs further elucidation. Some important questions which we are presently investigating are GGT in different age and sex groups and in abstainers, alcohol habits in individuals with normal GGT level, and relationships of GGT to other physical and biochemical variables, socioeconomical history, and retrospective and prospective morbidity.

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SERUM- γ -GLUTAMYLTRANSFERASE IN SCREENING AND CONTINUOUS CONTROL OF HEAVY DRINKING IN MIDDLE-AGED MEN

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Kristenson, H. (Dept. of Alcohol Diseases, Malmö General Hospital, S-214 01 Malmö, Sweden), E. Trell and B. Hood. Serum- γ -glutamyltransferase in screening and continuous control of heavy drinking in middle-aged men. *Am J Epidemiol* 1981;114:862-872.

In an on-going population study in Malmö, serum- γ -glutamyltransferase (GGT) is utilized both in biochemical screening of high alcohol consumption and as a tool in further investigation, treatment and control of middle-aged men with screening GGT in the top decile of the distribution. For this purpose, a special outpatient clinic has been instituted and is described in the present report. The composition of the intervention group and the feasibility of the program are reported for the first 6760 middle-aged male screening participants. A random one-half of the individuals with screening GGT in the top decile were allocated to the intervention group, which after primary dropouts and exclusion of concurrent diseases consisted of 252 individuals who have now been followed between three to six years. On the basis of structured interviews, hazardous levels of alcohol consumption were concluded to be present in 76% of the group. Although one-quarter of the group dropped out of the intervention program, the results indicate that it is feasible to institute an outpatient clinic for individuals with increased GGT levels found in a general health screening examination, to retain most individuals in this outpatient clinic and to consider alcohol habits and consumption levels in relation to the laboratory test value and general physical health status.

alcoholism; drinking behavior; gamma-glutamyltransferase; preventive health services

Serum- γ -glutamyltransferase (GGT) has been established as one of the most sensitive tests for early liver disorders (1, 2). In clinical studies GGT is elevated in alcoholism and heavy drinking (2, 3). The exact mechanisms of GGT elevation in heavy drinking are not known, but it has

been assumed that enzyme induction may be chiefly involved after chronic alcohol consumption (4, 5). We have studied GGT as part of a general preventive medical population study in Malmö, Sweden, since 1974 (6). In 72 per cent of apparently healthy middle-aged males with screening GGT in the top decile of the total GGT distribution, we have previously found that heavy drinking offered the most plausible underlying factor (6).

In recent literature, various methods of behavioral treatment and control of problem drinking and alcoholism have been reported (7, 8). Treatment of heavy drinking may prevent the development of overt alcoholism (9). Controlled social drinking is reported to be a relevant treatment goal in subgroups of alcoholics (10). The devel-

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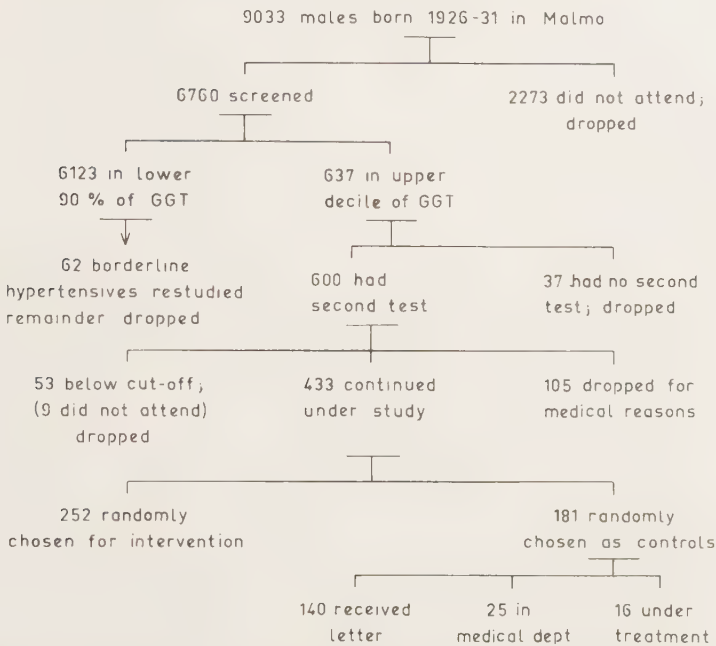


FIGURE 1. Study population: serum- γ -glutamyltransferase (GGT) in screening and control of heavy drinking in middle aged men. Among the controls, the 16 "under treatment" were being treated for previously known disorders when assigned to the control group.

opment of alcoholism is typically a protracted process. It should reasonably be of importance to intervene in the stages prior to the definite diagnosis.

We have been applying essentially the same principles in our population study since late 1974, by further investigation and treatment of individuals with increased GGT at screening in a special outpatient clinic within the Department of Preventive Medicine, Malmö General Hospital. In the present paper, we report on the design and feasibility of this program in middle-aged male birth-year cohorts in Malmö.

MATERIALS AND METHODS

Screening investigation

All male Malmö residents born in 1926-1931 were invited for examination at the Department of Preventive Medi-

cine, Malmö General Hospital, between the years 1974-1977. The details of this health screening have been given elsewhere (6). The participation rate in the six male birth-year cohorts was 75 per cent, corresponding to 6760 individuals (figure 1). At present about 17,000 individuals have been screened.

The examination is performed by nurses and comprises height- and weight-measurements, pulse and standing and recumbent blood pressure recording at 0 minutes and after 10 minutes' rest, skin-fold-measurement, simple pulmonary function tests, electrocardiogram recording and a number of (fasting) laboratory analyses including oral glucose tolerance test with glucose and insulin determinations. All laboratory analyses were performed according to standard methods at the Department of Clinical Chemistry,

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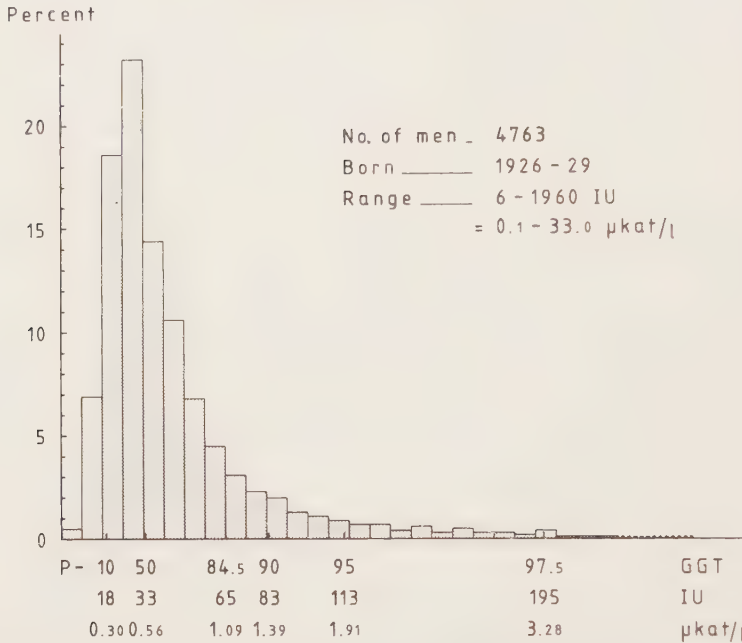


FIGURE 2. Screening serum- γ -glutamyltransferase (GGT) distribution in 1926-1929 male birth year cohorts. The 10th, 50th, 84.5th, 90th, 95th and 97.5th percentiles (P) are indicated. The normal range of GGT in this age- and sex-group at our laboratory during the time of study was $\leq 1.08 \mu\text{kat/liter}$, corresponding to the 84.5th percentile of the GGT distribution in the screening material.

Malmö General Hospital. Serum- γ -glutamyltransferase (GGT) is analyzed according to the recommendations of the Scandinavian Enzyme Committé (11).

Controls with GGT below 90th percentile

Of the male 1926-1931 birth-year cohorts with screening GGT value below the top decile of the distribution, 62 members were chosen. These subjects were randomly selected from a group of individuals with borderline arterial hypertension but below the GGT cut-off point for intervention and receiving no medical treatment. They were attending the Department of Preventive Medicine each year for blood pressure determinations, and were interviewed and investigated regarding alcohol habits in the same way

as the individuals referred to the outpatient clinic described below.

Controls with GGT in top decile

Figure 2 represents the total GGT distribution in the male screening participants born in 1926-1929. Individuals with screening GGT in the top decile of the screening GGT distribution (corresponding to $>1.65 \mu\text{kat/liter}$ in the 1926 birth-year cohort and $>1.40 \mu\text{kat/liter}$ in the 1927 birth-year cohort, when the method was slightly modified) were invited for a second determination of the GGT value within three weeks. The reason for the second test was to exclude cases with erratic GGT values. If this value was also found to be above the cut-off point the individuals were assigned on

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a random basis as a control group or referred to the outpatient clinic.

The second test also excluded some individuals with GGT just above the cut-off point at the screening but just below this level at the second test; on the whole there were relatively few losses in the control groups (figure 1). In the 1926 birth-year cohort individuals with systemic hypertension, latent diabetes or hyperlipidemia were excluded, but from the 1927 birth-year cohort systemic hypertension cases were referred to the hypertension clinic for special treatment (figure 1).

The remaining men were assigned as controls if they had even birthday *and* even birthmonth or uneven birthday *and* uneven birthmonth. Initially, a small subgroup of 25 controls was referred to the medical clinic for detailed investigation including liver biopsy (table 1). The rest were informed by letter that they had an impaired liver. They were told in the letter to live as usual, but to be careful with alcoholic beverages, and that they would receive an invitation for another liver test after two years. Understandably, some of these individuals, especially if there were borderline abnormalities in some other test value such as serum triglycerides, etc., asked for further investigation and treatment, and were then excluded from the control group; the others were invited by letter after two years for a repeat GGT-test at the Department of Preventive Medicine.

Outpatient clinic

Individuals with two consecutive GGT values in the top decile and even/uneven constellation of birthday/birthmonth or birthmonth/birthday were allocated to an intervention group and invited for further assessment at the Department of Preventive Medicine. Additional liver tests were performed and a general physical examination and history were obtained as well

as an interview designed to elicit a detailed drinking history.

Symptoms of alcohol dependence were recorded and the criteria specified by the US National Council on Alcoholism were used (12). Information was requested as to development of increased tolerance to alcohol, withdrawal symptoms, morning drinking, loss of control and inability to abstain. Dietary habits, medication and exposure to organic solvents were also evaluated. The relevant socioeconomic, marital and occupational status, and earlier disease history were obtained from demographic files and the medical questionnaire and updated during the personal interviews.

At the first consultation, which lasted approximately one hour, interest was initially focused on neutral subjects and then shifted to more sensitive topics. The purpose was to establish a relationship with the individual so as to understand his life situation and evaluate his personal difficulties and problems. Usually, several visits were needed to get a clear picture of the alcohol consumption pattern and magnitude. But a preliminary estimation of consumption was made at the first visit and discussed in relation to the elevated GGT value. A treatment goal of moderate drinking rather than abstinence was agreed upon. Heavy drinkers were asked to lower their overall consumption and to abstain for at least two days a week from every kind of alcoholic beverages in order, as was explained, to let their liver and other organs recuperate somewhat.

Moderate daily drinking was postulated to damage the liver more seriously than relatively heavy weekend consumption with abstinence five days in between. The patients were instructed to note the extent of their social alcohol consumption as well as to identify the circumstances which characteristically led to excessive drinking. Even the subjects with elevated

GGT values who did not admit to alcohol consumption were recommended to come for intervention; some of them later admitted to moderate or heavy drinking and were treated as described above.

All patients were offered continuing outpatient follow-up with half-hour consultations with the same physician every third month and in between GGT tests and reinforcing contacts with the same nurse every month. The subjects were carefully informed of the GGT level at every check-up and reminded to lower their alcohol consumption to get GGT below the cut-off point. Some patients stopped drinking completely for three weeks, and noting their decreasing GGT, were gradually convinced of the value of continuous check-ups. Treatment emphasis was placed on gradual, steady improvement rather than rapid but variable change. Generally, no drugs were used and the patients were fully able to work, but a few subjects reported sleeping disturbances and anxiety. They received minor tranquilizers for a few weeks and were in more close contact with the nurse. Individuals who after repeated consultations would not cooperate or who in spite of several letters did not attend were considered dropouts.

After a few visits the responders reported decreasing drinking and the GGT values were reduced as well. The patients were encouraged to develop interests in hobbies and physical exercise. When the GGT value had stabilized at an acceptable level the contacts with the therapists were gradually spaced at longer intervals. However, the patients had at least two visits a year with the physician and at least two additional visits with the nurse for check-ups and laboratory determinations. The treatment was originally planned to go on for at least two years. Most patients are still in treatment, and the follow-up period is intended to be five years.

RESULTS

In figure 2, the distribution of screening GGT is shown in the male 1926-1929 birth-year cohorts.

Figure 1 shows the background population, screening participants, and number of individuals with screening GGT exceeding the cut-off level chosen to correspond to the top decile of the distribution. Figure 1 also summarizes various dropout categories and individuals referred for other treatment or randomized into controls; 252 individuals remained for the intervention group.

Table 1 shows the results of the alcohol consumption interviews in the intervention group (252 histories) and the group with GGT below the 90th percentile (62 histories). In the first group, heavy alcohol consumption was concluded to be present in 54 per cent, moderate alcohol consumption in 22 per cent and light alcohol consumption in 19 per cent. Nonusers were 5 per cent. (Ninety per cent of those who subsequently dropped out of the intervention group were classified as heavy drinkers). Hazardous drinking levels were concluded to be present in 76 per cent of the intervention group.

In the GGT-normal group, which presumably reflects the general population of male screening participants in these birth-year cohorts, heavy alcohol consumption was indicated in 15 per cent, moderate in 25 per cent and light alcohol consumption in 50 per cent; nonusers were 10 per cent (table 1).

In the intervention group, alcohol was found to be the main factor behind the increased GGT in 191 cases (75 per cent). Other possible factors were found mainly in the light consumers and nonusers. Medicines were rather frequent possible factors (20 cases, 8 per cent) and a high consumption of "rapid" carbohydrates was also noted in a number of these individuals ($n = 12$, 5 per cent). Nonalcohol liver disease was uncommon, found in six

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TABLE 1

Alcohol consumption in the intervention group and the normal serum- γ -glutamyltransferase (GGT) group

Alcohol consumption category	Intervention group		Normal GGT group	
	No.	%	No.	%
Heavy (>40 g/day)	136	54	9	15
Moderate (20–40 g/day)	55	22	16	25
Light (<20 g/day)	48	19	31	50
Nonusers	13	5	6	10
Total	252	100	62	100

TABLE 2

Symptoms of alcohol dependence (%) in alcohol and probable alcohol subgroups of the intervention group, and in the normal serum- γ -glutamyltransferase (GGT) group

	Alcohol and probable alcohol groups (<i>n</i> = 206)	Normal GGT group (<i>n</i> = 62)
	%	%
Tolerance	59	13
Withdrawal symptoms	30	2
Morning drinking	20	2
Loss of control	9	0
Inability to abstain	3	0

cases (2 per cent) of the whole intervention group. These cases were investigated at the Department of Medicine and there were three with unclear hepatopathy, one case of biliary cirrhosis, one case of hepatic carcinoma and one with dystrophia myotonica and impaired liver function. Organic solvents offered a possible explanation in four cases (2 per cent). In 19 cases of the intervention group (8 per cent) the cause of GGT elevation was unknown.

Table 2 compares symptoms of alcohol dependence in 206 members of the intervention group with alcohol or probable alcohol cause of the GGT elevation, with the GGT-normal group. In the former individuals symptoms of dependence, in particular increased tolerance to alcohol, were frequent, while in the latter group such symptoms were exceptional.

Tables 3 and 4 represent comparisons of the occupational and the marital status in the intervention group males born be-

tween 1926 and 1929 with various matched subgroups. These include subsamples of individuals in the same birth-year cohorts with strictly median (GGT 0.56–0.59 μ kat/liter, *n* = 140) screening GGT values and nonattendants to the screening born in 1926–1929 (*n* = 179). In occupational composition, there are no remarkable differences apart from an underrepresentation of individuals with disability pension in the median GGT subgroup (0 per cent) and overrepresentation in the intervention group (5 per cent; of the cases later dropping out of the program, 13 per cent had disability pension). In marital status, the most notable difference was an overrepresentation of divorced individuals in the intervention group (particularly in the dropouts, 29 per cent) and the nonattendants, in which there was also an increased frequency of unmarried men.

Table 5 summarizes the results in the 24 months' follow-up of the intervention

TABLE 3
Occupational composition in intervention group and random subsamples born in 1926-1929

	Disability pension: %	Unskilled manual: %	Semiskilled manual: %	Skilled manual: %	Foreman: %	Senior clerk: %	Managerial position: %
Median group: 0.56-0.59 μ kat/liter (n = 140)	0	27	11	21	5	29	7
Intervention group (n = 170)	5	13	13	23	12	27	7
Screening nonattendants (n = 179)	2	18	17	26	6	24	7

group: 169 of the 252 males in the total intervention group remained in treatment; of the 83 losses 48 were dropouts (19.1 per cent), 30 had been referred to other clinics and five (2.0 per cent) had died.

Table 6 compares the mean GGT values in 145 members of the intervention group still in treatment after two years with 113 controls who were invited by letter to obtain a GGT-test two years after their screening examination. There is a significant decrease of the GGT value in the intervention group individuals and there is a slight tendency of decreased mean GGT value also in the controls, but this difference is not statistically significant. The initial GGT (which in both groups is the mean of the screening and the subsequent check-up GGT value) is comparable in both groups.

The reason why the major attempts up till now have been made in males 46-49 years old (about 12,000) was that our planning was made within the framework of tackling the major middle-aged cardiovascular risks in these age-groups. We have, however, with some slight modifications followed the same approach within male birth-year cohorts born between 1938 and 1944. In the cohorts of males born in 1938 and 38 years old at the time of screening, the minimum length of follow-up is now three years. The experiences seem on the whole to be similar to those in 8-10-year-old males and thus rather encouraging. So far, however, the data do not allow more exact evaluation in this age group.

DISCUSSION

Our study supports earlier conclusions that in a well-defined population GGT may be utilized as a marker of alcohol intake (6, 13-15). In middle-aged males participating in our general medical screening investigation, GGT levels in the top decile of the distribution were associated with hazardous drinking levels

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TABLE 4
Marital status in 1977 for intervention group and comparison groups born in 1926-1929

	% unmarried	% married	% divorced	% widower
Average, Malmö males	11	77	12*	
Intervention group (n = 170)	9.5	72	16.5	2
Screening nonattendants (n = 179)	23	54	21	2

* Percentage of combined categories, divorced and widowed.

TABLE 5
*Results in the 24 months' follow-up
of the intervention group*

	No.	%
Intervention group	252	100
Remaining after 24 months	169	67
Losses within 24 months	83	33
Dropouts 0-12 months	34	13.5
Dropouts 13-24 months	14	5.6
Referred to other clinics*	30	11.9
Deaths†	5	2.0

* Referred to other clinics: 5 to Hypertension Clinic, 2 to Lipid Clinic, 2 to Diabetes Clinic, 10 to Medical Clinic, 7 to Alcohol Clinic and 4 to other clinics.

† Five causes of death, which occurred 12-23 months after screening: myocardial infarction, suicide, pancreas cancer, liver cancer, and pancreatitis.

in 76 per cent (65 per cent heavy consumption, 11 per cent moderate consumption) of the cases. In most of them, alcohol consumption was the predominant cause of the GGT elevation; and symptoms of alcohol dependence were prevalent in the group, in comparison with a random subsample of individuals with screening GGT below the 90th percentile.

However, apart from a few differences in terms of number of persons divorced, who were overrepresented in the males with increased screening GGT (particularly those dropping out of the intervention program), there were no major differences in the occupational or marital composition of the intervention group in comparison with other population subsamples or the general population. Thus, GGT by and large would seem to identify social drinkers in the population.

This does not mean that GGT identified insignificant drinking habits. Since the days of the "temperance tales" (16) and through Jellinek's pioneering studies (17), it has been known that the peak of the "drunkards progress from the first glass to the grave," or, in Jellinek's terminology, the crucial phase of the development to overt alcoholism (18), is typically in middle age. Furthermore, careful investigation in our intervention group revealed clinical symptoms of alcohol dependence in one-half of the individuals (table 2). We have also elsewhere reported that individuals with elevated GGT in the screening examinations are characterized by considerably more retrospective sickness cash benefit days in the years prior to screening than individuals with low GGT (19), and also, in general, exhibit a higher frequency of abnormal health screening tests in their somatic health profile than individuals with low GGT (20).

We therefore believe that the identification of individuals with elevated GGT in our screening investigation carries preventive implications. Earlier studies of GGT in populations have not investigated the further utilization of GGT as an instrument in treatment and control of heavy alcohol consumption identified by the test. In our program, we also use GGT as a tool in subsequent individual treatment and prevention. Our methodology of information, motivation, feedback and biochemical control, focused on the abnormal liver test and the somatic health state in relation to alcohol consumption, is in agreement with behavioral therapy principles (7, 8).

TABLE 6

*Initial (mean of screening and check-up values) and 24 months' GGT in all cases in the intervention group remaining in treatment after 2 years, and all controls who responded to the invitation for rescreeing with GGT 2 years after the initial test**

	No.	Initial GGT		24 months' GGT		0-24 months' difference: <i>t</i> -test
		$\bar{m}$	SD	$\bar{m}$	SD	
Intervention group	145	2.68	1.78	1.99	1.17	$t = 3.90$ $p < 0.001$
Controls	113	2.69	1.95	2.25	2.53	$t = 1.46$ (NS)

* $\bar{m}$, mean value, SD, standard deviation. The *t*-test expresses the statistical significance of the difference between the initial and 24 months' GGT in each group separately.

Studies in controlled drinking have been performed in recent years (10, 21). For the most part, alcoholic inpatients have been assigned to behavioral treatment with moderation as a goal and compared to patients with traditional treatment and abstinence as a goal. In a study by Pomperleau et al. (22), groups of middle-income outpatient problem drinkers (total number = 32) were randomly assigned to one of two treatments: a multicomponent positive reinforcement procedure emphasizing moderation, or traditional denial confrontation therapy emphasizing abstinence. The subjects were on average 44 years old and had an educational and economic background which gave them a more favorable prognosis than most people currently undergoing treatment for alcohol problems (22). The serum- γ -glutamyltransferase level was determined and showed a significant correlation with self-reported drinking levels. Of the seven participants who had abnormally elevated GGT values prior to treatment and who reported a substantial decrease in consumption between screening and the end of treatment, six individuals showed a corresponding decrease in enzyme activity at the end of therapy.

The present study groups are derived from a general population of 46-48-year-old males by means of elevated GGT values and consist of a mixed population

of alcoholics, heavy and moderate social drinkers and uncertain cases. We have focused our interest on continuous supervision of the individuals and especially on the GGT values since information given about alcohol consumption and drinking habits does not seem to be particularly trustworthy.

In our opinion, the preliminary results of the program are encouraging with the majority of the individuals still remaining in the outpatient clinic after two years or more, and showing improved GGT levels.

Our study indicates that it is feasible to institute an outpatient clinic for individuals with increased GGT levels found in a general health screening examination, to retain these individuals in this outpatient clinic and to discuss their alcohol habits and consumption levels in relation to the laboratory test values and general physical health status. However, it is well known that the nonattendant group in population investigations (in our study amounting to 25 per cent) has a higher frequency of alcohol-related problems than the participants (23, 24). Thus, our findings and conclusions are by necessity restricted to the participating part of the population. However, our aim was to institute a treatment and control program in screening attenders identified as heavy drinkers by means of careful investiga-

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tion of increased GGT. In this situation, the main problem is that in close to one-third of the individuals the elevated screening GGT was not associated with alcohol as the predominant underlying factor. They represent a diversity of probable or tentative causes. The relation between certain medicines, in particular hydantoins and barbiturates, and GGT elevation seems well established (1, 25) and was incriminated in 24 individuals in our study population.

There is also a possible relation to factors like overweight and high carbohydrate consumption with or without hypertriglyceridemia (1, 26), which appeared plausible in 16 cases. Nonalcoholic liver disease was surprisingly infrequent in the subjects, noted in only six cases. One of these was a case of dystrophia myotonica with reduced liver function, the pathophysiology of which is unknown (27). The liver cancer case was histologically of the angiosarcoma type.

The identification of other health problems by means of GGT may of course also be of value. However, it is apparent that the evaluation and treatment of a high level of GGT found in general health screening cannot be generalized in an individual case, and requires a considerable amount of time and professionalism. Even though the short-term feasibility results seem promising it would be premature to claim any definite success until long-term results, such as morbidity and mortality figures, and comparisons with various control and nonresponding groups are available. These studies are under way.

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SERUM FERRITIN, GAMMAGLUTAMYL-TRANSFERASE AND ALCOHOL CONSUMPTION IN HEALTHY MIDDLE-AGED MEN

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Summary

Serum ferritin was analysed in 169 middle-aged men. Ninety-one were heavy drinkers with increased serum gammaglutamyltransferase (GGT) values in otherwise normal routine screening tests; 39 were from the same birth year cohorts with normal GGT values; and 39 were teetotalers. Increased ferritin values were found in 67% of the heavy drinkers, but only in 2.5% in the two other groups. The mechanisms of the serum ferritin elevation in otherwise healthy alcohol over-consumers are unknown, but heavy drinking should be taken into consideration in the interpretation of increased serum ferritin values in individual cases.

Introduction

Serum ferritin concentration has been reported to be proportional to the iron stores in the body [1]. Thus in iron-deficiency anemia when iron stores are depleted serum ferritin is low, whereas in iron overloading such as hemochromatosis or hemosiderosis serum ferritin is high. High serum ferritin is also seen in acute and chronic inflammation, in liver disease without evidence of increased iron stores, in certain neoplastic disorders, and in conditions associated with increased red cell replacement [2 - 4]. However, all of these conditions are relatively rare in a population of subjectively healthy middle-aged men, in which high serum ferritin values should therefore be relatively uncommon.

After the original report of Szczeklik *et al.* [5] of serum gammaglutamyltransferase (GGT) in liver disease several studies of GGT have verified their findings and found GGT also to be influenced by alcohol consumption [6, 7]. We have studied serum GGT levels in middle-aged men in Malmö,

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who were invited to a health screening investigation, and have found heavy drinking associated with about 70% of the individuals in the highest GGT decedile [8]. Since the serum concentration of both GGT and ferritin is increased in alcohol liver disease, we speculated that ferritin might be increased also in this group of heavy drinkers even in the absence of manifest liver disease. As controls we have used males from the same birth year cohorts with GGT in the 50th percentile and male teetotalers.

Material

Between November 1974 and 1978, middle-aged male birth year cohorts in Malmö, born in 1926 - 1931, were invited to a health screening at the Department of Preventive Medicine, Malmö General Hospital. The participation rate was 75%, corresponding to 6750 individuals. A random subsample ($n = 270$) of individuals with a screening serum GGT activity $>1.4 \mu\text{kat/l}$ * was invited for further evaluation and treatment at a special outpatient clinic, where a detailed history of the alcohol consumption was obtained by one of the authors (H. K.). The results have been published elsewhere [8]. In about 70% of the individuals, the predominant factor behind the elevated GGT value was judged to be alcohol, and 60% were classified as heavy drinkers. For the present study a subsample of this group of heavy drinkers was used. All had serum GGT activity $>1.4 \mu\text{kat/l}$. Their estimated ethanol consumption was 80 ± 46 g per day (mean $\pm$ SD, range 35 - 250, $n = 91$). Three cases in this group had alcohol liver cirrhosis.

Two other groups were studied:

(1) Thirty-nine 48-year old males randomized from the same birth cohorts as the heavy drinkers but with serum GGT activity in the 50th percentile ($0.54 - 0.58 \mu\text{kat/l}$).

(2) Thirty-nine middle-aged male members of the International Order of Good Templars in Southern Sweden. Their mean age was 48.8 years (38 - 55 years). GGT was $0.54 \pm 0.35 \mu\text{kat/l}$ (mean $\pm$ SD).

All the individuals in these two groups as well as in the heavy drinking group were characterized by unremarkable general health screening results. Apart from the three liver cirrhosis cases, no one had signs of overt liver disease, neoplastic disease, overt gastrointestinal disorders, inflammatory conditions or manifest anemia in the routine screening tests.

Methods

Plasma was obtained in the morning after an overnight fast. The routine analyses were performed within 24 h after sampling at the Department of Clinical Chemistry, Malmö General Hospital. Gammaglutamyltransferase activity [9], and the activity of alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) [10] were determined according to the recom-

* $\mu\text{kat/l} \approx 60$ I.U.

recommendations of the Scandinavian Enzyme Committee. Serum iron was determined on a Varian model AA-775 atomic absorption spectrophotometer. Total iron-binding capacity (TIBC) was determined immunologically [11] as transferrin using a commercial standard serum (Seronorm Protein, Nyegaard & Co) as standard.

Ferritin analyses were done on plasma samples which had been kept at -20°C for 12 - 36 months. Ferritin was determined according to Halliday *et al.* [12] and was isolated from human spleen [13] as standard. The anti-serum was used to coat small polystyrene tubes (AB Medart, S-54065 Lyrestad, Sweden). Specific antibodies were isolated by affinity chromatography on ferritin linked to CNBr-activated Sepharose 4 B (AB Pharmacia, Uppsala, Sweden). The isolated antibodies were labeled with ^{125}I by the lactoperoxidase method of Thorell and Johansson [14]. The working range of the method was 2.5 - 40 $\mu\text{g/l}$ and the between-days coefficient of variation was 17% at the level of 46 $\mu\text{g/l}$. The normal range was 15 - 400 $\mu\text{g/l}$.

Results

Figure 1 shows the screening GGT distribution in middle-aged males in Malmö. There is an obvious shift to the right. The upper decentile of the screening GGT distribution corresponds to 1.4 $\mu\text{kat/l}$, while the upper normal reference value for GGT in this age group at our laboratory is 1.0 $\mu\text{kat/l}$. About 15% of the apparently healthy, middle-aged males who attended the voluntary screening investigation had values above this limit.

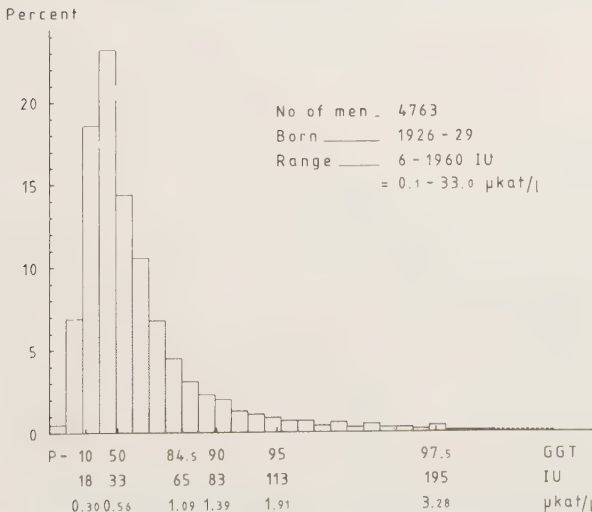


Fig. 1. Screening GGT distribution in male birth year cohorts 1926 - 1929 ($n = 4763$). The values are expressed in both international units (I.U.) and $\mu\text{kat/l}$. P = percentile.

The serum concentrations of the various analyses from the three groups are shown in Table 1. Serum iron was significantly higher in the high GGT group where about 50% of the individuals had values above the normal limit. TIBC was similar in all three groups.

Ferritin concentration was significantly higher in the high GGT group; 67% of the individuals in this group had values greater than 400 $\mu\text{g/l}$ but only one in each of the two other groups (Figs. 2 and 3). ASAT and ALAT concentrations were elevated ($>0.7 \mu\text{kat}$) in 35% and 51% of the individuals in the high GGT group, giving a mean value slightly above the normal limit for both enzymes. The GGT level was increased in all these individuals, in one case up to 30 times the upper normal limit.

There was no simple relationship between daily alcohol intake and ferritin concentration (not shown), nor was there any linear correlation between GGT and ferritin (Fig. 2). Three of the individuals in the high GGT groups had known liver cirrhosis, two of whom had normal ferritin levels. Apart from high GGT, high alcohol consumption and in some cases ALAT

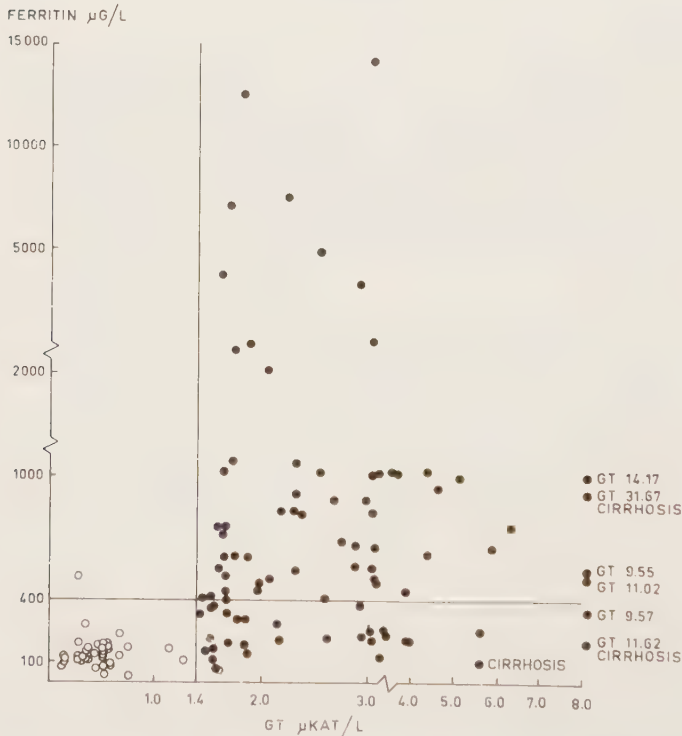


Fig. 2. Serum GGT ($\mu\text{kat/l}$) and ferritin ($\mu\text{g/l}$) in 91 middle-aged males with screening GGT in the upper decedtile and heavy drinking confirmed by interview (full circles), in comparison with 39 middle-aged male members of the International Order of Good Templars in Southern Sweden (open circles).

TABLE 1

Serum concentration in different analyses from heavy drinking-high GGT groups, median GGT groups and teetotalers (the normal range is given for comparison)

	Serum iron ($\mu\text{mol/l}$)	TIBC ¹ ($\mu\text{mol/l}$)	Ferritin ($\mu\text{g/l}$)	GGT ² ($\mu\text{kat/l}$)	ASAT ³ ($\mu\text{kat/l}$)	ALAT ⁴ ($\mu\text{kat/l}$)
High GGT groups	30.0 ± 10	71 ± 14	1238 ± 2263	3.36 ± 3.75	0.80 ± 1.24	0.94 ± 1.43
Median GGT groups	11 ± 4	75 ± 15	228 ± 623	0.56	ND ⁵	ND
Teetotalers	12 ± 4	72 ± 16	134 ± 80	0.54 ± 0.35	ND	ND
Normal range	10 - 28	45 - 72	15 - 400	<1	<0.7	<0.7

¹ TIBC = total iron-binding capacity.

² GGT = gamma-glutamyl transferase.

³ ASAT = asparagine aminotransferase.

⁴ ALAT = alanine aminotransferase.

⁵ ND = not determined.

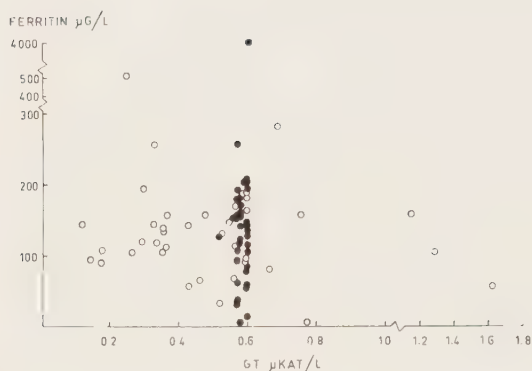


Fig. 3. Comparison of serum GGT ($\mu\text{kat/l}$) and ferritin ($\mu\text{g/l}$) in 39 middle-aged male members of the International Order of Good Templars in Southern Sweden (open circles), and 39 forty-eight year old males randomized from the same birth year cohorts as the heavy drinkers but with serum GGT activity in the fiftieth percentile (full circles).

and/or ASAT elevations, the screening findings and health status of these individuals were generally normal.

The low GGT groups and the teetotalers were in general very similar in all other screening tests. All but one of the teetotalers had low serum ferritin values and only one of them had a GGT value greater than $1.4 \mu\text{kat/l}$. The two groups are distinctly separated in both serum ferritin and GGT distribution (Fig. 2). The serum ferritin values in the median GGT group were very similar to those of the teetotalers (Fig. 3), but the mean value was higher (Table 1).

Discussion

There is currently a rising interest in biochemical indicators of alcohol consumption in the population. Several laboratory tests are influenced by alcohol consumption, *e.g.* GGT, transaminases, urate, triglycerides and mean corpuscular volume, blood pressure *etc.* Of these, GGT seems to be one of the most sensitive and it has been widely used as a marker of heavy drinking in population studies [15 - 19].

Our findings demonstrate that serum ferritin levels are elevated in 67% of apparently healthy middle-aged males with increased values of GGT and documented heavy alcohol consumption, but without any other signs of liver disease or manifest blood, gastrointestinal or inflammatory disorders. In chronic non-cirrhotic alcoholics, elevated serum iron concentration was a common finding on admission but a normalization occurred after abstinence for 1 - 3 weeks [20]. None of these patients showed signs of anemia nor B_{12} or folate deficiencies.

Similarly, our data show increased serum iron concentration in the group with high GGT and heavy drinking, but without anemia or, in most

individuals, any signs of liver disease. TIBC was normal in all these individuals giving a transferrin saturation of 42% mean. We think that in the majority of the individuals the probable explanation for the increased ferritin level is the heavy drinking. The reason for the increasing ferritin concentration and the origin of the ferritin that accumulates in the serum of the heavy drinkers are not known. In individuals with strictly normal GGT values we found but one individual with high serum ferritin. In the teetotalers the findings were similar.

This may indicate that serum ferritin can be utilized as an indicator of alcohol consumption in a population. Individuals with strictly normal GGT or with documented alcohol abstention only exceptionally showed increased ferritin, but individuals with increased GGT and documented alcohol overconsumption had elevated serum ferritin levels in 67% of the cases. In chronic alcoholism elevated serum ferritin levels have been reported [21]. The main interest of the findings in the present study is that increased serum ferritin values are clinically often taken to indicate various hematological, gastrointestinal or inflammatory disorders or overt liver disease [3], while our findings indicate that heavy alcohol consumption may increase serum ferritin levels markedly in otherwise apparently healthy persons. This should be taken into consideration in the interpretation of increased serum ferritin values in individual cases.

Acknowledgements

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INDICATORS OF ALCOHOL CONSUMPTION

COMPARISONS BETWEEN A QUESTIONNAIRE (Mm-MAST),
INTERVIEWS AND SERUM γ -GLUTAMYLTRANSFERASE (GGT)
IN A HEALTH SURVEY OF MIDDLE-AGED MALES

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SUMMARY

A questionnaire consisting of nine questions about drinking habits was used in a preventive program for middle-aged males in Malmö. With a cut-off point of two yes-answers to the questions, 66 per cent of a group of heavy drinkers, 73 per cent of all registered alcoholics and 90 per cent of not previously identified alcoholics were identified. Serum γ -glutamyltransferase (GGT), used as an indicator of heavy alcohol consumption in the screening, was a poor instrument for the detection of alcoholism in the same population, assigning correctly only 35 per cent. In combination, the two tests identified 82 per cent of all registered alcoholics, and 97 per cent of the alcoholics who were registered in the period following the screening investigation. Thus Mm-MAST is a useful screening test for alcoholism in medical screening examinations and may successfully be used in combination with biochemical tests.

INTRODUCTION

Since Selzer in 1971 introduced the Michigan Alcoholism Screening Test (MAST) it has shown to be applicable to hospital patients (1-5). With modifications a shortened version of MAST, the brief MAST and a Self Administered Alcoholism Screening Test (SAAST) have also been used in general medical populations (6-7).

In our screening investigation (8) of apparently healthy middle-aged males in Malmö we use an extensive questionnaire and from April 1976, nine alcohol questions ("Malmö modification of the brief MAST"; Mm-MAST) have also been included. In order not to upset the individuals we choose questions about attitude and customs rather than of serious symptoms. The questions were on purpose not particularly penetrating and no weighing of responses or attempt to bias responses towards admitting problems were made. The main purpose of the screening study was to use serum γ -glutamyltransferase (GGT) in screening for alcoholrelated disabilities and heavy drinking and make use of the Mm-MAST as a supplement.

Below the findings of Mm-MAST in different groups of the middle-aged male screening population in Malmö, particularly in alcoholics and heavy drinkers are reported. Furthermore, the results are compared with biochemical indices and a semistructured interview of drinking habits.

MATERIAL AND METHODS

Malmö is a southern Swedish city of 235 000 inhabitants. All male Malmö residents born in 1926-1931 ($n = 9\ 033$), were invited to an investigation at the Department of preventive Medicine, Malmö General Hospital, between the years 1974-1977. The details of the health screening have been given elsewhere (8). The participation rate in the six male birth year cohorts was 74.8% corresponding to 6 750 individuals. The alcohol questions (Mm-MAST) were not given until april 1976 and include a few males born in 1927 and all screening participants born in 1928-1931 ($n = 4\ 350$).

The screening investigations comprise several physical and laboratory investigations, including GGT (9). An oral glucose tolerance test is performed and during this test, the attendants answer the questionnaire in relative privacy and relaxation. This was presented by a box system according to Collen (10), where the questions on each card were assorted in "yes"-, "no"- or "don't know"-sections of the box. The nine alcohol questions were presented among the other in a random order. The question "Are you a teetotaler?" was included to get an approximative frequency of abstainers in the population. The nine Mm-MAST questions are represented in Table 1.

Figure 1 gives the design of the investigation. The participants (P) compose different groups I-IV.

- I Birth year cohort born 1928 ($n = 1\ 187$). The Mm-MAST was analysed in detail.
- II Normal GGT group ($\text{GGT} < p\ 90$). A subgroup with screening GGT value below the top decentile of the distribution ($n = 58$). These individuals were randomly selected from a group of individuals with a slightly elevated high blood pressure but below the cut-off point for intervention. They were attending the Department of Preventive Medicine every year to check the blood pressure, and were interviewed in the same way as group III; 41 could be classified as light drinkers or nonusers (NA), and 17 (A) were classified as moderate ($n = 7$) or heavy ($n = 10$) alcohol consumers according to the same criteria as in that group. Their alcohol consumption was 52 ± 15 g/day (mean $\pm$ s.d., range 40-80 g/day).
- III Heavy drinkers. Half of the individuals with screening GGT values in the top decentile of the distribution ($> 1.40\ \mu\text{kat/l}$), ($\text{GGT} > \frac{p90}{2}$), who were invited to a special out-patient clinic for investigation of their alcohol habits and who after semistructured interviewing were classified as heavy drinkers ($n = 125$). Their mean consumption of alcohol was 84 ± 44 g/day, (mean $\pm$ s.d., range 30-300 g/day).

Table 1 Total number of yes-answers to question of abstaining and different Mm-MAST questions in 4 350 middle-aged men at screening and GGT percentiles ($\mu\text{kat/l}$) in each group

	Answers		GGT percentiles*		
	N	%	P 50	P 90	P 95
A. Are you a teetotaler?	286	5.8	0.39	0.96	1.61
1. Do you take a drink before going to a party?	714	14.5	0.51	1.59	2.28
2. Do you usually drink a bottle of wine or corresponding amounts of alcohol over the week-end?	1 122	22.7	0.49	1.38	2.08
3. Do you drink a couple of drinks (or beers) a day to relax?	240	4.8	0.67	2.45	4.55
4. Do you tolerate more alcohol now than you did ten years ago?	395	8.0	0.47	1.77	2.43
5. Have you difficulties not drinking more than your friends?	137	2.8	0.49	1.56	2.33
6. Do you fall asleep after moderate drinking without knowing how you got to bed?	227	4.6	0.51	1.24	1.80
7. Do you have a bad conscience after drinking?	347	7.0	0.49	1.72	2.49
8. Do you take a drink (a beer) the day after a party?	667	13.5	0.51	1.52	2.24
9. Do you try to avoid alcoholic beverage for a determined period of time e.g. a week?	805	16.3	0.49	1.49	2.36

* For the whole background population the GGT median was 0.56 $\mu\text{kat/l}$ and the P 90 and P 95 1.40 $\mu\text{kat/l}$ and 1.91 $\mu\text{kat/l}$ respectively. Hence the GGT distribution was skewed to the left in the teetotalers, but to the right in the other groups.

- IV All participants who were still living in Malmö and who had at least once been admitted to and registered at the Department of Alcohol Diseases (RAD), between 1968-1979 ($n = 223$). Of these, 31 were registered in the years 1977-1980, that is, after they had participated in the screening investigation.

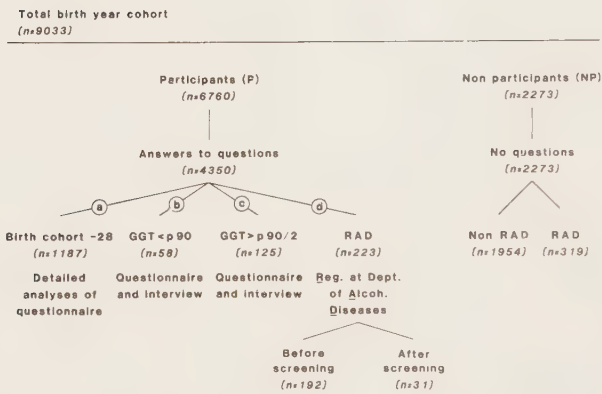


Figure 1. Study material

During the interviews symptom of alcohol dependence were also evaluated (11). Dietary habits, medications and exposure to organic solvents were analysed as well. In 73 per cent of individuals with screening GGT in the top decetile, alcohol was incriminated as the probable main cause (8, 12).

RESULTS

Of the total population of middle-aged men born in 1926-1931, 706/9033 (8%) were alcoholics registered at the Department of Alcohol Diseases. As expected there was a higher frequency of alcoholics in the non-participant group than in the participants, 14 versus 6%. However, nearly half of the registered alcoholics attended to the health screening investigation and answered the questionnaire.

Table 1 shows the Mm-MAST questions, number of yes-answers to the different questions, and the GGT values ($\mu\text{kat/l}$) of the 50th, 90th and the 95th percentiles of the GGT distribution in those responding to the respective questions. Altogether, the 4 350 individuals gave 4 940 yes-answers: 5.8% answered affirmatively to the question "Are you a teetotaler?" In this group the lowest GGT values were found. The question 3 "Do you drink a couple of beers a day to relax?" is interesting since GGT is considerably higher in all percentiles in this question as compared to the others.

The number of yes-answers given in the different study groups are summarized in Table 2. Group I is representative for the whole population and shows that 29 per cent of the individuals had two or more yes-answers. The figures are practically the same in the GGT normal group, while 73 per cent of the alcoholics responded to two or more of the questions and so did 66 per cent of the heavy drinkers. The mean answers per individual, which was 1.1 in the total population, were 2.9 and 2.4, respectively, for the alcoholics and the heavy drinkers, and 0.9 for the individuals with normal GGT. If one takes together individuals with moderate and heavy alcohol consumption found in this group, there were 17 such individuals (A) while the rest had light alcohol consumption or were non-users (NA). The results of the screening and the questions were kept unknown for the interviewer until after the interviews. The only obvious fact was that the individuals in the GGT normal group had GGT values below the 90th percentile of the GGT distribution. If the questionnaire results are compared in the A and NA groups it is seen that 16 of 17 individuals in group A corresponding to 94 per cent answered

Table 2 Numbers of yes-answers to Mn-MAST in the study groups

Group	Born 1928 n = 1187 I		GGT normal n = 58 II		Heavy drinkers n = 125 III		Alcoholics n = 223 IV		GGT normal A n = 17		GGT normal NA n = 41	
	n	%	n	%	n	%	n	%	n	%	n	%
Teetotaler?	55	5	3	5	0	0	6	3	0	0	3	7
0 yes-answers	461	38	31	54	18	14.5	22	10	0	0	31	76
1 yes-answers	328	28	6	10	25	20	32	14	1	6	5	12
2 yes-answers	174	15	11	19	24	19	45	20	10	59	1	2.5
more than 2 yes-answers	169	14	7	12	58	46.5	118	53	6	35	1	2.5
Number of answers per individual	1.1		0.9		2.4		2.9					

two or more questions, while 2 of 41 (5 per cent) individuals in the MA-group answered two or more questions.

These results can be utilized for calculating the diagnostic sensitivity and specificity* of the Mm-MAST in relation to alcoholism and heavy drinking. With a cut-off level of two yes-answers, the diagnostic sensitivity of the questionnaire is 66 per cent in relation to heavy drinking and 73 per cent in relation to alcoholism. The diagnostic specificity as obtained from the individuals with low alcohol consumption in group II may be as high as 95 per cent.

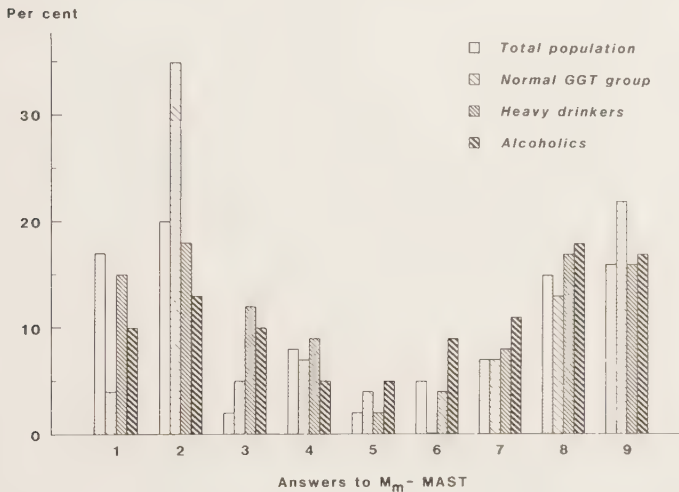


Figure 2 Answers to the Mm-MAST questions in the study groups. The columns represent the frequency of individuals answering yes to the questions.

In Figure 2, the frequency of yes-answers to the Mm-MAST questions are compared in the different study groups. On the whole, there is a similar distribution of yes-answers in the subgroups as compared to the total cohort of males born in 1928, but there are significant differences in

* Sensitivity: The proportion of cases positive on the test
Specificity: The proportion of non-cases negative on the test

the relative frequencies of each question in the groups. However, the figure illustrates that the results in the single questions are not conclusive, but the amount of yes-answers may be correlated to the results of the other indicators of the alcohol consumption.

Table 3 Per cent of the study groups in different screening GGT brackets

	Laboratory reference level < 1.04	Laboratory reference level 1.05-1.39	Screening top decetile >1.40
Total population	83	7	10
Normal GGT group	97	3	(0)
Heavy drinkers	-	-	(100)
Alcoholics	62	7	31
Alcoholics (registered after screening)	65	13	22

Table 3 compares the GGT levels in the registered alcoholics in the screening population with the findings in the general population. Only 22-31 per cent of the alcoholics had GGT values in the top decetile of the screening distribution. Even if the GGT cut-off point is lowered to the upper normal reference level (1.08 μ kat/l, approximately corresponding to 65 IU) only 7-13 per cent more of the alcoholics are identified, indicating a low sensitivity of the test.

To test if yes-answers to Mm-MAST could have any social relevance to alcoholism we counted the total days of hospital care during five years for a subgroup of the alcoholics registered at the Department of Alcohol Diseases. Individuals giving affirmative positive answers to two or more questions had 41 days of inpatient care for the period compared to 20.5 days for the individuals with 0 and 1 answer. This indicates that the alcoholics report valid information to the questionnaire and that

the low answer group is in better social adjustment than the other group.

DISCUSSION

The original MAST correctly assigned 98 per cent of hospitalized alcoholics and only 15 out of 526 individuals scored as non-alcoholics on the MAST were revealed as alcoholics by the record search (1). The brief MAST was equally effective (6). In a recent community study from Glasgow (12) the brief MAST excluded a considerable number of persons identified on other tests as being alcoholics. The authors conclude that the brief MAST is not suited for use outside clinical populations. In contrast, our modification of the brief MAST which indicates ordinary drinking habits, identified 73 per cent of the individuals which were at the time of screening registered at the Department of Alcohol Diseases. In comparison, GGT identified only 31 per cent of the registered alcoholics, which suggest that GGT is not a sensitive indicator of alcoholism in a health screening investigation. This may of course be due to selective factors; only half of the alcoholics took part in the screening and these may predominantly represent alcoholics temporarily in an abstaining period, and 3 per cent of them answered yes to the teetotaler question.

However, the Mm-MAST misclassified 24% of the registered alcoholics. The combination with GGT may increase the diagnostic sensitivity, since there were 13 individuals with high GGT values which could reduce the false negatives to 18 per cent. This is still a rather high figure and should possibly be explained by the weak and undefined questions. Furthermore, if the diagnostic sensitivity in a combination of tests is increased the consequence is a lower specificity.

28 of 31 of the alcoholics (90 per cent) who were registered after screening had answered yes to two or more questions. This corresponds to a prospective sensitivity of the Mm-MAST practically as good as the original MAST. There are about 30 per cent of the general population, who will answer yes to two or more questions. This is high, but in the normal GGT group only 5 per cent could be classified as false positives. Conversely, there were 6 per cent false negatives.

Furthermore, in the heavy drinkers with elevated screening GGT, 66 per cent answered yes to two or more questions. This indicates that the sensitivity of Mm-MAST in social heavy drinking is of about the same magnitude as the GGT and might explain a substantial part of the 30 per cent positive results in the whole population.

Recently a study in 1 002 consecutive patients receiving general examinations indicated that SAAST could identify alcoholism in a local residential population (14). Our questionnaire could be used in healthy middle-aged males to identify both heavy social drinkers and some alcoholics. The data of the present study clearly indicates, however, that GGT is not suited as an indicator for alcoholism in a population screening. With a combination of questionnaire and biochemical tests like GGT, a larger part of heavy drinkers, and possibly also alcoholics might be identified. If the Mm-MAST and GGT results were combined in those alcoholics who were registered after the screening investigation, no less than 97 per cent of them could be identified. This points to a future possibility of utilizing a combination of questionnaire and different biochemical tests for identification of heavy drinkers and alcoholics in screening investigations.

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CONVICTIONS FOR DRUNKENNESS OR DRUNKEN DRIVING
SICK ABSENTEEISM AND MORBIDITY IN MIDDLE-AGED MALES
WITH DIFFERENT LEVELS OF SERUM- γ -GLUTAMYLTRANSFERASE

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SUMMARY

In a continuous population study of middle-aged males in Malmö, serum- γ -glutamyltransferase (GGT) has been utilized both as a biochemical indicator of alcohol consumption and as an aid in further investigation and treatment. The individuals in the top decentile of the GGT distribution have been compared to individuals in other GGT brackets. The number of individuals with legal convictions for drunkenness or drunken driving was 2.8 times larger in the top decentile of GGT as compared with those below the median. The corresponding ratio for drunken driving alone was 3.4. The number of sick days was analysed for 1 290 individuals in a longterm study over 21 years before screening and random subsamples with different GGT values were compared. Increasing GGT values were correlated with the disability rate over all years. There was a dramatic rise in the occurrence of sick days during the six years before screening in the top decentile of GGT. Conversely 50 per cent of the individuals below the median on GGT had less sick absenteeism than the mean for all Swedish males throughout the 21 years before screening.

Morbidity was analysed in a three year subsample study of 285 individuals with 90 sick days during the most recent years. The ratios of disability between the individuals in the highest and lowest decentile of the GGT distribution were highest in the diagnostic groups injuries (5.5) and mental disorders (4.3).

It is concluded that in groups of individuals with high GGT values an accumulation of alcohol related disabilities is present.

INTRODUCTION

We have previously described a research screening program aimed at identification and intervention of the most important health risks in middle-aged males, i.e. hypertension, hyperlipidemia, impaired glucose tolerance and high alcohol consumption (12). Apparently healthy men were invited to a planned screening investigation which was free of charge and 75 per cent of the invited population participated. Serum- γ -glutamyl-transferase (GGT) levels were used to trace heavy drinkers and to motivate them to controlled drinking (13). A random half of the screening participants with GGT in the top decentile of the GGT distribution was chosen as an intervention group. In this group heavy drinking was found to be the most plausible cause of elevated GGT values in 72 per cent of the subjects (12). The other half of the individuals in the GGT top decentile was followed as a control group. Further details on convictions for drunkenness and drunken driving, longterm sick leave and morbidity prior to the screening investigation are reported. The individuals in the top decentile of the GGT distribution are compared with the individuals in other GGT brackets of the screening population. The purpose is to correlate alcohol related parameters of social behavior with a marker indicative of alcohol consumption, the GGT.

MATERIAL AND METHODS

In this report we have studied three parameters: convictions for drunkenness and drunken driving; distribution of sick days from 1955 to 1975; and diagnoses in recent morbidity of more than 90 sick days during 1973-1975. The design is given in Tables 1-3.

GGT was analyzed in all males by standard methods (27). The upper normal laboratory value was $= 1.08 \mu\text{kat/l}$. The median was $0.56 \mu\text{kat/l}$ and the lower limit of the top decentile was $1.40 \mu\text{kat/l}$.

The Chi-square method was used for calculating statistical significance. The usual chi-square test with one degree of freedom was used for testing differences between relative frequencies in two groups while differences between the number of occurrences of events (e.g. convictions) in two

Table 1 CONVICTIONS FOR DRUNKENNESS AND DRUNKEN DRIVING (STUDY A)

Middle-aged men attending screening born 1926-1927	Random subsamples of GGT distribution Half of the top Controls below decimile the median	
n = 2 403	n = 112	n = 112

Table 2 TOTAL SICK DAYS 1955-1975 (STUDY B)

Middle-aged man attending screening born 1926-1927 n = 4 667

Random subsamples of GGT distribution

Low GGT group

I the lowest decimile n = 257

Intermediate group

II at the median n = 253

III above the median n = 255

IV moderately elevated n = 243

n = 751

High GGT group

V the top decimile n = 286

Table 3 MEN WITH RECENT MORBIDITY OF > 90 SICK DAYS 1973-1975 (STUDY C)

further selection from study B

Low GGT group	35/257	(13.6%)
Intermediate group	157/751	(20.9%)
High GGT group	93/290	(32.0%)

groups were tested by means of a test conditional on the total number of occurrences.

A Convictions for drunkenness and drunken driving

Information was collected from the records of the Inland Revenue Register about all convictions for drunkenness during 1942-1976. As the registration was not available for all subjects, subsamples from our first two birth year cohorts were selected.

Drunkenness is considered present when public behaviour under intoxication leads to arrest. Drunken driving offenses are differentiated into two classes: drunken driving (blood alcohol level 150 mg% or more) and driving under the influence of alcohol (more than 50 mg% but less than 150 mg%).

A total sample of 112 individuals born in 1926 and 1927 with screening GGT values in the top decile was compared with a random sample of 112 participants from the same birth year cohorts with GGT values below the median.

B Distribution of sick days from 1955 to 1975

The national sick insurance system covers all residents. Cases of work incapacity on grounds of sickness are automatically reported to the social insurance office. Illnesses lasting more than seven days must be certified by a physician. In many cases the diagnoses are preliminary and unclear. With the aim of creating equally large groups of individuals with GGT, in various ranges, 25 per cent of males born between 1926-1929 (1 294 of 4 667) were selected for this longterm study.

The ranges used were:

- I the lowest decile
- II at the median
- III above the median
- IV between upper normal laboratory value and top decile
- V the top decile of the distribution

In the last-mentioned group we collected data for all individuals with two consecutive high GGT values. From the original random group of 286 individuals with screening GGT in the top decentile, 89 were excluded either by not attending the second check up or having a second GGT value below 1.40 μ kat/l. We therefore added 93 individuals from subsequent screening with two consecutive GGT in the top decentile yielding a total of 290 cases in this high GGT group (185 in the intervention subgroup and 105 in the control subgroup).

From the Insurance Office in Malmö data about sick days were collected for about 25 per cent of the 4 667 screening participants, randomly distributed in the defined subgroups (Table 5). The total number of sick days per year was registered for a period of 21 years (1955-1975). In the intervention group, an evaluation of drinking habits had previously been performed allowing a differentiation into subgroups of individuals with alcoholic (A), probably alcoholic (PA) and non-alcoholic (MA) etiologies (13).

To characterize the frequency and duration of sick absenteeism frequency distributions were constructed from the number of periods of sick leave, total number of sick days and various ratios were computed. Three of these were the frequency, disability and severity ratios (5, 16, 20) defined as follows:

$$\text{Frequency} = \frac{\text{Number of periods of sick leave}}{\text{Number of persons}}$$

$$\text{Disability} = \frac{\text{Number of sick days}}{\text{Number of persons}}$$

$$\text{Severity} = \frac{\text{Number of sick days}}{\text{Number of periods of sick leave}}$$

C Diagnoses in recent morbidity of more than 90 sick days during 1973-1975

We analysed morbidity in the different GGT groups during the three years before screening. Both the medical diagnoses on the certificates as well as the durations of the illnesses were checked. As the mean disability

for 1976 was 28 days for men 45-50 years old in Malmö (18) we decided to look in detail at all individuals who had more than 30 sick days per year or in total more than 90 days for the three years of interest (1973-1975). In addition, the frequency of zero sick leave and disability of less than 30 days were analysed for the three years for comparison. In this part of the study a small group of non-participants in the screening program (n = 179) selected at random and patients registered at the Department of Alcohol Diseases (RAD) (n = 80) during the years 1969-1979 from the same birth year cohorts were also included. Annual taxable income for the year 1977 was examined for all groups. The diagnoses for all 285 subjects with high morbidity during the three years were grouped and coded according to the International Classification of Diseases (ICD) (9). Disability in the major diagnostic categories was compared between this group and the different GGT groups as well as the RAD group.

RESULTS

A Convictions for drunkenness and drunken driving

Of the high GGT group 33.0 per cent (37/112) had been registered with convictions for either drunkenness, drunken driving or driving under the influence of alcohol. For the control group the figure was 11.6 per cent (13/112). Table 4 shows that among the 25 individuals in the high GGT group there were 224 convictions for drunkenness compared with 21 for the 12 individuals in the control group. Of the individuals in the high GGT group, three had respectively 56, 55 and 49 convictions and another six had 3 or more. In the control group one individual had 6 convictions. Thus the individuals in the high GGT group had about 10 times as many convictions for drunkenness per man compared with the controls.

Sixteen individuals in the high GGT group had 27 offences of drunken driving compared with 4 individuals with 5 offences in the control group. Thus the incidence of drunken driving convictions in the high GGT group was about 5 times that in the controls.

TABLE 4 CONVICTIONS FOR DRUNKENNESS, DRUNKEN DRIVING AND DRIVING UNDER THE INFLUENCE OF ALCOHOL IN HIGH GGT GROUP AND CONTROL GROUP

	Convictions for drunkenness (CD)			Drunken driving		Driving under the influence of alcohol	
	Number	Individuals	Individuals with more than 2 CD	Number	Individuals	Number	Individuals
High GGT group	224	25	9	27	16	12	11
Control group	21	12	1	5	4	5	4
Ratio	10.7	2.1	9.0	5.4	4.0	2.4	2.8
Significance of ratio	p<0.001	p<0.05	p<0.01	p<0.001	p<0.01	-	-

B Distribution of sick days from 1955 to 1975

TABLE 5 TOTAL SICK DAYS 1955-1975 IN RELATION TO GGT-LEVEL FOR MALES
ATTENDING SCREENING BORN 1926-1929

	GGT μ kat/l	Total sick days	Indivi- duals	Disability	
				Mean	Median
Group I	0.01-0.29	46 765	257	182	84
Group II	0.56-0.59	63 587	253	251	108
Group III	0.70-1.03	74 358	255	292	130
Group IV	1.05-1.38	89 576	243	369	147
Group V (random)	>1.40	146 720	286	513	191
Group V (total)	2x>1.40	147 698	290	509	

Table 5 gives the total disability for the different GGT groups at random. For the total period of 21 years there is an accumulation of days in the high GGT group with 146 720 days over the years compared with the low GGT group which had 46 765 days. The higher the GGT value the higher mean and median for the different groups. The disability in the low GGT group was 182 days (mean) and 84 days (median) compared with 513 days (mean) and 191 days (median) in the high GGT group.

The disability for the total group of individuals with high GGT as well as the group with moderately raised GGT values was compared with the general development of disability for all males in Sweden (1955-1975) and also compared with the GGT group below the median (Figure 1). Part of the high GGT group (185 of the 290 individuals) had been chosen for intervention. Men in this group participated in frequent counselling and GGT controls as a motivation for limited drinking. This project and results are described elsewhere (13). The disability from the subgroups of the

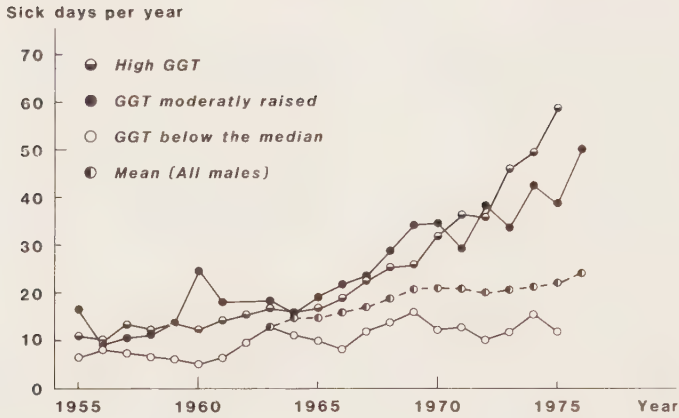


Figure 1

All individuals with two high GGT's ($\text{GGT} > 1.40 \mu\text{kat/l}$, $n = 290$), individuals with moderately raised screening GGT's ($n = 67$ mean $1.9 \pm 0.10 \mu\text{kat/l}$, range $1.05 - 1.38$) and individuals with screening GGT below the median for the total distribution ($< 0.56 \mu\text{kat/l}$, $n = 100$) during 21 years before screening are compared with Swedish figures for males from the National Social Insurance Board of Sweden. Individuals with disability pension are counted as 365 days per year.

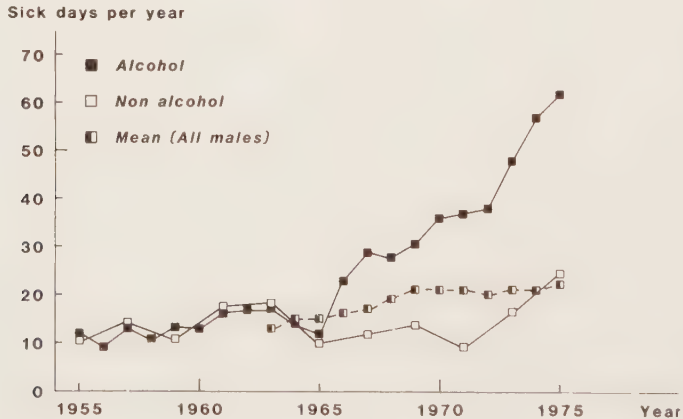


Figure 2

Individuals with two high GGT values ($\text{GGT} > 1.40 \mu\text{kat/l}$) in the intervention group who had been categorized as alcohol $n = 100$ or non alcohol $n = 39$ are compared with Swedish figures for all males.

intervention group NA and A were also compared with the same general population during the 21 years (Figure 2). As seen in Figures 1 and 2 the average male in Sweden in 1963 had a disability of 12 days with a gradual increase to 25 days 1975. In Malmö 1976 the disability was 28 days for males aged 45-50 (18).

The GGT group below the median had "subnormal" sick absence throughout the years with a very limited absolute increase. The group with moderately raised GGT values, the high GGT groups and the alcohol (A) group of the intervention group demonstrated the same general increase during the previous ten years although the degree of disability was different. The A group had a "supernormal" and rapidly rising disability throughout the 21 years before screening. The NA group had low sick absenteeism up to a few years before screening.

The disability increased continuously (182-303-509 days) through the different GGT groups and in the total high GGT group the disability was 509 days which is practically the same as 513 days in the random high GGT group (Table 5). The number of disability pensions increased from 0 per cent in the low GGT group to 3.1 per cent in the high GGT group. The same trend was seen in the RAD group increasing from 1.5 per cent in the low GGT group to 16.9 per cent in the high GGT group, while the annual income decreased from 68 000 to 56 000 swedish crowns respectively (Table 6).

Table 6 TOTAL SICK DAYS 1955-1975, DISABILITY; PENSIONERS, INDIVIDUALS REGISTERED AT THE DEPARTMENT OF ALCOHOL DISEASES (RAD) AND ANNUAL INCOME FOR DIFFERENT GGT GROUPS

	Total sick	N	Disability	Pensioners	RAD	Annual income thousand crowns 1977
GGT groups						
Low 0.01-0.29 µkat/l	46 765	257	131	0	4	68 ± 25
Intermediate 0.56-1.38 µkat/l	227 521	751	303	13	46	60 ± 19
High 2 x > 1.40 µkat/l	147 698	290	509	9	49	56 ± 16

Table 7 MARITAL STATUS IN INDIVIDUALS WITH MORE THAN 90 SICK DAYS IN DIFFERENT GGT GROUPS GIVEN IN PER CENT OF THE GROUP

GGT groups	Unmarried	Married	Divorced	Widower
Low	6	91	3	-
Intermediate	7	75	18	-
High	14	55	28	3

2 Sick absenteeism in insured members

A picture of impaired social adjustment in the high GGT group is shown in the marital status (Table 7). The frequency, disability and severity in absenteeism were calculated for the individuals with 90 sick days during the three years before screening (Table 8). The disability increased from 207 in the low GGT group to 354 in the high GGT group. The frequency was 7.2 in the low and 8.7 in the high GGT group. Finally the severity which was 29 days in the lowest group gradually increased to 31 in the intermediate group and to 41 days in the high GGT group. Also the number of total sick days for the period 1973-1975 is shown. These days constituted 34 per cent of the total days in each group for the years 1955-1975.

Table 8 INDIVIDUALS WITH MORE THAN 90 SICK DAYS 1973-1975 FOR DIFFERENT GGT GROUPS AND NON PARTICIPANTS (NP)

GGT groups	Total days	N	Disability	Frequency	Severity
Low	7 271	35	207	7.2	29
Intermediate	42 204	157	268	8.7	31
High	32 980	93	354	8.7	41
NP	19 702	46	428		-

Of the non-participants 46/179 individuals (25.7 per cent) had high morbidity. The disability was 428 days or double that of the low GGT

group (207 days), being the highest of the study groups. The high GGT group, however, had 93/290 individuals (32.0 per cent), with 90 sick days and thus somewhat higher frequency than the non participants. In general the non-participant group most resembled the high GGT group but the range in disability and income was larger indicating that this group was the most heterogenous and should be analyzed separately. This group may well contain both the healthiest and the most poverty stricken individuals in the total population.

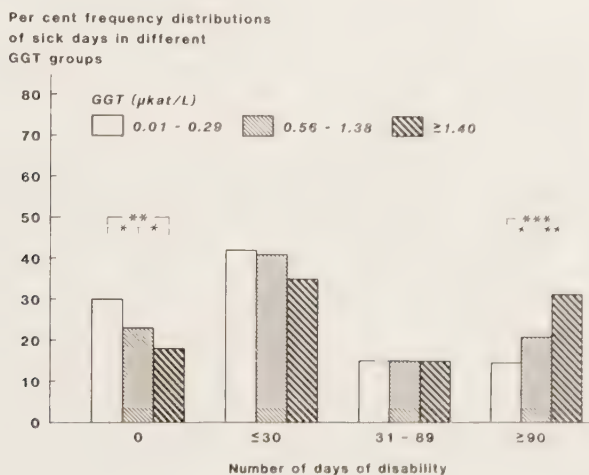


Figure 3

Per cent disabled for zero days, less than 30 days and more than 90 days during three years before screening are compared within different GGT groups. Chi square $P < 0.1$ * $P < 0.01$ ** $P < 0.001$ ***

Figure 3 gives the frequency of individuals with zero sick days, less than 30 days and more than 90 days over the three years. The most remarkable finding is that 30 per cent of the individuals in the low GGT group had no sick absence at all compared with 18 per cent of the individuals in the high GGT group. On the other hand 14 per cent in the low GGT group had more than 90 days compared with 32 per cent in the high GGT group. The differences in incidence of zero sick days and 90 sick days are statistically significant.

D Diagnoses in recent morbidity

In analyzing the causes of disability it was necessary to contend with some inaccuracies in the reported diagnoses. The problem is greatest for short term absences not requiring a physician's certificate where the diagnoses are based on symptoms reported to the insurance office by the individual. The problem is even greater for alcoholics. Short term absenteeism resulting from alcoholic intoxication or hangovers are probably reported as some common minor disorder such as cold or gastrointestinal upset. In this study, a diagnosis of alcoholism was reported in only 18 absences accounting for a total of 351 sick days. All of these individuals were registered at the Department of Alcohol Diseases.

The total disability in different ICD groups are given for 285 individuals in Table 9. Of a total 85 528 sick days, musculo-skeletal disorders was the most common category with 32.4 per cent of the days. Mental disorders came second with 19.1 per cent followed by injuries with 12.7 per cent of the total days. Respiratory diseases which include the common cold and minor infections was the fourth category, (12.0 per cent) followed by digestive disorders (10.1 per cent) and cardiovascular disease (7.3 per cent). All the other diagnostic groups were very small. Tumours accounted for only 0.5 per cent of the sick days and no days were categorized as hematologic disorder.

Disabilities for the main diagnoses in the different GGT groups are pronouncedly different as seen in Table 10. The ratios between the high and the low GGT group were highest for injuries with 5.5 and mental disorders with 4.3. For respiratory diseases the ratio was 2.7 and for gastrointestinal diseases 2.0 while for cardiovascular and musculo-skeletal diseases the differences were very small (0.9 and 1.3 respectively). Remarkable was that the RAD had the highest disability rate with 122 days in mental disorders and only 6 days in the cardiovascular disease, while the low GGT group had 10 days in urogenital diseases (the highest of all groups) and also 104 days in musculo-skeletal diseases.

TABLE 9 MORBIDITY AMONG ALL INDIVIDUALS (n = 285) WITH MORE THAN 90 SICK DAYS 1973-1975

ICD groups	Sick days	Per cent
I Infective and parasitic diseases	548	0.6
II Tumours	398	0.5
III Endocrine, nutritional and metabolic diseases	792	0.9
IV Diseases of the blood and blood-forming organs	0	0
V Mental disorders	16 354	19.1
VI Diseases of the nervous system and sense organs	959	1.1
VII Diseases of the circulatory system	6 237	7.3
VIII Diseases of the respiratory system	10 238	12.0
IX Diseases of the digestive system	8 663	10.1
X Diseases of the genito-urinary system	898	1.1
XII Diseases of the skin and subcutaneous	664	0.8
XIII Diseases of the musculo-skeletal system	27 679	32.4
XVI Symptoms and ill-defined conditions	1 214	1.4
XVII Accidents, poisonings and violence	10 884	12.7
	85 528	100.0

Table 10 DISABILITY IN DIFFERENT ICD GROUPS, IN 285 INDIVIDUALS WITH MORE THAN 90 SICK DAYS, FOR THE DIFFERENT GGT GROUPS AND ALL INDIVIDUALS REGISTERED AT THE DEPARTMENT OF ALCOHOL DISEASES (RAD)

Diagnoses ICD group	Inter-			RAD	Ratio High/Low
	Low	mediate	High		
V mental	18	54	78	122	4.3
VII cardiovascular	17	26	16	6	0.9
VIII respiratory	19	30	52	40	2.7
IX digestive	21	25	42	30	2.0
X urogenital	10	1	4	3	0.4
XIII musculo-skeletal	104	73	135	167	1.3
XVII injuries	8	41	44	48	5.5

DISCUSSION

In the present report convictions for drunkenness or drunken driving, sick days and morbidity have been used as indicators of alcohol-related disabilities. The number of individuals who had been registered with convictions for drunkenness or drunken driving was 2.8 times larger in the high GGT group than the control group. Since the individuals in the high GGT group had about 10 times as many convictions for drunkenness as the controls the study indicates that serious alcohol problems are considerably more common among individuals with high screening GGT values ($\text{GGT} > 1.40 \mu\text{kat/l}$) than in the individuals with GGT values below the median ($\text{GGT} = 0.56 \mu\text{kat/l}$). In a study of male disability pensioners it has been shown that one third had been convicted for drunkenness (14). The social consequences of alcohol abuse expressed as having entered official registers are highly correlated to alcoholism and alcohol abuse as defined in medical terms (10). More than half of the offenders who are sentenced for drunken driving appear to be habitual alcoholics (31). In the present study 24 per cent (27/112) of the individuals in the high GGT group had been sentenced for drunken driving compared with 7 per cent (8/112) of the controls. As the ratio of

those sentenced for drunken driving in these two groups was 3.4 it seems reasonable to conclude that individuals with elevated GGT values have an accumulation of alcohol-related disabilities.

The total number of sick days 1955-1975 for the high GGT group was 146 720 being 3.1 times that for the low GGT group (46 765). Using the disability (mean and median) for these extreme groups the ratios were 2.8 and 2.2 respectively. The disability over the years strongly indicates that alcohol consumption is the main cause for the difference in sick absenteeism in these sex and age uniform groups. The GGT value at screening correlates positively with the disability during many years before screening. On the other hand half of the individuals below the median of the GGT distribution had fewer sick days than the mean for all Swedish males throughout the 21 years prior to screening.

In the investigation of recent morbidity the differences between the groups were even more pronounced. Thus 35/257 (14 per cent) of the individuals in the low GGT group had a disability of more than 90 sick days compared with 93/290 (32 per cent) in the high GGT group. This does not imply, however, that all individuals in the high GGT group had high sick absenteeism. On the contrary not less than 53 per cent of the individuals in the high GGT group had less than 30 sick days during the three years. In the low GGT group this fraction was 72 per cent. Thus a GGT value in the top decentile of the GGT distribution indicates a high disability to the group but not necessarily for its single individuals.

GGT is one of the tests which have been most widely used in screening for alcoholism in clinical and population studies (3, 6, 12, 15, 19, 24-26, 29, 33-35). Correlation between GGT levels and drinking habits have been reported (3, 6, 12, 19, 34, 35) although there was also a negative report (24). We have previously shown that 72 per cent of the men with GGT values in the top decentile of the GGT distribution could be classified as moderate to heavy drinkers (12). In the present study these individuals compose the probably- (PA) and the alcoholics- (A) groups. The other 28 per cent of the individuals or the non-alcoholic- (NA) group. Data on sick days and drinking habits were evaluated independently. Thus the high GGT values often reflect significant and longterm sick absenteeism and for the majority of the men

in this study the disabilities are alcohol-related. Although heavy drinking seems to be the most common cause of elevated GGT level in men, it is not specific to heavy alcohol consumption. Drugs, in particular antiepileptics and barbiturates (7, 26), obesity (22, 29) and exposure to organic solvents (13) are related to elevated GGT. In liver disorders (1, 2, 30), hypertension (4, 8, 11, 23, 28) and rheumatoid arthritis (17) the GGT level might also be raised. GGT has also been used in calculating risk factors for premature death in middle-aged men (21). Thus elevated GGT levels should be taken seriously and lead to careful investigation including evaluation of drinking habits in individual cases. The preventive implications of these findings are presently under investigation.

Sick absenteeism has been studied in different materials of alcoholics and controls (5, 16, 20, 27). In a study by Bjerver in Stockholm, Sweden, ten years (1956-1965) of morbidity were analyzed. He found 3.8 times more sick days for alcoholics compared to the controls. The mean age for both groups was 46 years. The distribution of diagnoses was similar to that found in the present study.

In the study of Pell and D'Alonzo sick absenteeism of 764 alcoholics during a one year period was compared with that of a control group of 863 non-alcoholics. The disability was 13.0 days per person per year among the alcoholics and 5.8 days among the controls. Absenteeism of the alcoholics was greater than that of non-alcoholics in all major diagnostic categories except for disorders of the urinary system. The excess among the alcoholics was greatest for injuries, musculo-skeletal disorders and digestive diseases.

In our study the ratios of disability between the high GGT and low GGT group were highest in injuries (5.5) and mental disorders (4.3). The Pell and D'Alonzo study discussed the sick absenteeism in a large group of employees and we studied the disability in different GGT groups of healthy men. Although the studies are not comparable in details the general results are very similar. More than half (53 per cent) of the individuals in the high GGT group had a low sick absenteeism in our study. Slightly more than half of the alcoholics in the Pell and D'Alonzo study also had an acceptable attendance record for the year. All individuals in the high GGT group are

clearly not alcoholics and high sick absenteeism is characteristic for only half of the individuals in populations with alcohol-related disabilities.

Thus in this study the individuals with high GGT levels have a high incidence of alcohol-related disabilities: registered drunkenness, drunken driving, registration at the Department of Alcohol Diseases and high absenteeism, with significant personal and economic implications. Although this is typical of the group it should be remembered that many individuals in the group are free from these characteristics.

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HOSPITALIZATION AND ALCOHOL RELATED MORBIDITY
WITHIN THREE YEARS AFTER SCREENING IN MIDDLE-AGED MEN

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SUMMARY

All men living in Malmö born 1926-1929 were invited for a health screening examination which included among many other things measurement of γ -glutamyltransferase (GGT). They were followed up and within three years after the screening 963 of 4 571 men had been hospitalized. They obtained 17 158 hospital days, an average of about 6 days per individual and year.

The impact of alcohol on the admissions was analysed both according to the International Classifications of Diseases and a new design where all the diagnoses were grouped and coded in conditions which were judged to be alcohol related, potentially alcoholinfluenced and non-alcohol-related. Of the total days alcohol psychosis and alcoholism made up 13.6 per cent. Close to thirty (29.2) per cent of the days were caused by alcohol related and potentially alcoholinfluenced conditions.

GGT values at the screening investigation were significantly increased in 25 per cent of the hospitalized men.

Alcohol related admissions were seven times as many in men with GGT values in the highest quintile compared with those which had values in the lowest quintile.

INTRODUCTION

Morbidity studies among alcoholics overwhelmingly indicate that the health hazards associated with alcohol are considerable (1, 2). Quantitative information is lacking to assess the impact which alcohol exerts on specific diseases as well as on many common illnesses (2). Admissions to psychiatric hospitals for alcohol disorders have increased in Britain in the last 25 years by a factor of 25(3). In Malmö the incidence of delirium tremens increased 38 per cent during 1974-1976 (4) and in another study the fracture incidence was about four times as common in alcoholics as in controls (5). In the present health screening and intervention in Malmö serum- γ -glutamyltransferase (GGT) is used not only as a screening instrument, but also as a tool in continuous control of heavy drinkers (6). The relation between levels of GGT at screening and premature death in middle-aged men has been reported (7). Heavy alcohol consumption was the single most important factor associated with premature death and GGT values at the screening investigation were significantly increased in 46 per cent of those who died.

This report concerns the extent and causes of hospitalization within three years follow-up for 963 men. The days of hospital care for alcohol-related disorders were estimated. A certain group of illnesses that might be influenced by alcohol consumption have been analysed in relation to the GGT values at the screening investigation. Finally the number of firmly diagnosed alcoholics has been calculated.

MATERIAL AND METHODS

In Malmö (235 000 inhabitants), besides longterm care facilities, there is one psychiatric hospital with 560 beds and one general hospital with 1 600 beds, including a Department of Alcohol Diseases. Since 1975 all hospital admissions are computer-recorded. Individual identifications, day for admission and discharge, department, one to three diagnoses per admission and some procedures (operation and autopsy) are registered. Coverage of hospital days was complete because of financial reasons but not of diagnoses depending on doctors' delay. In this study at least

80 per cent of the diagnoses were covered. Only the first diagnosis at every admission was analysed. The information for the years 1975-1979 was used.

From October 1974 to May 1976 all male Malmö residents born 1926-1929 were invited to the screening investigation at the Section of Preventive Medicine at the Department of Internal Medicine. Non-attendants to the screening in the first birth year cohort, men born 1926, were reinvited one year after the first screening period (June 1976), but in the other birth year cohorts the men were invited a second time immediately after the first screening period was ended. Thus there were three years follow up for all attendants except a small part (16 per cent) of the birth year cohort born 1929.

Of totally 6 180 men born 1926-1929, 4 571 or 74 per cent attended the screening examination. 963 of these or 21 per cent had been admitted to hospital at least once and practically all admissions, except the cases of chronic psychosis, were at the general hospital. For comparisons a small group of non-attendants to the screening investigation was included. In a random subsample (n = 200 of 1 609 non-attendants) 54 individuals or 27 per cent had been hospitalized.

All hospital admissions, days and diagnoses were collected from the computer. The hospital days and first diagnoses were coded and grouped according to the International Classification of Diseases (ICD) (8). Besides this classification the morbidity was divided in three new categories:

- I Illnesses considered to be directly related to excessive drinking; Alcohol related conditions (ARC). These were: Alcohol psychosis (291), Alcoholism (303), Abstinence-epilepsy (345,09), Intoxication with ethanol (980), Liver cirrhosis (571,00) and Pancreatitis (577). Pancreatitis in combination with cholelithiasis was excluded.
- II A certain group of illnesses known to be more common in alcoholics or to be possibly related to excessive drinking. Potentially alcohol

influenced conditions (PAIC). It comprised the following diagnoses: Pulmonary tuberculosis (0,11), Oesophageal and laryngeal cancer (150, 161), Gout (274,00), Neurotic and Psychosomatic disorders (300, 305), Epilepsy (345:10, 98, 99), Neuritis and Polyneuritis (352, 354:08, 09, 357), Hypertension and Cardiomyopathy (401,99, 425,09), Thrombophlebitis and Thrombosis (451, 453), Oesophageal varices (456), Pneumonia (485, 486), Gastritis and peptic ulcer (531-535), Hepatitis (571:01, 573), Symptoms from nervous system and digestive tract (780, 784:50, 785:10, 30, 51), Observations (793,99), Fractures: skull, nose rib, pelvis, femur (800,00, 802,00, 807,00, 808,00, 821,00), Commotio (850,00), Burns (941-949) and Unfavourable influence of drugs (965, 967, 970, 972, 978, 979). These conditions were selected from the ICD and might be more or less influenced by alcohol consumption. It is recognized that the composition of this group might be subject to different opinions.

III All other diagnoses; Not alcohol related conditions (NARC)

The 963 hospitalized men were classified according to the diagnostic categories (ARC, PAIC, NARC). Each individual was classified once but he could have several admissions with days in the different categories. Those men who had at least one admission in the ARC or PAIC group were included in the respective group, the rest was grouped into the NARC.

The hospital records of the Department of Alcohol Diseases between 1969-1979 were also searched. Of the 963 men 175 (18 per cent) had been registered there at least once during this period. In general a registration indicates drinking problems for about ten years. Half of the registered are being classified as chronic alcoholics.

The distribution of the screening GGT values in the total screening cohort of males born 1926-1929 was divided in quintiles and the screening GGT values of the hospitalized men were grouped in these quintile classes. In the lowest quintile (GGT 0.18-0.35 $\mu\text{kat/l}$) there were 15 per cent and in the highest (GGT > 1.00-31.5 $\mu\text{kat/l}$) 25 per cent of the men. The top decile got 16.5 per cent. This means that the probability of being hospitalized in the lowest quintile was 0.75 and in the highest 1.25. The statisti-

cal significance of deviations from an even distribution in the quintile classes was calculated by the CHI^2 method.

RESULTS

Within three years after the screening examination 963 of the 4 571 screening attendatns had obtained in total 17 158 hospital days, that is 17.8 days per individual or practically 6 hospital days per individual and year.

According to the ICD mental disorders were the most common category with 31.8 per cent of the total hospital days. In this group (2330/5449 days) or 13.6 per cent of the total days were caused by alcohol psychosis and alcoholism. The other 3 119 days in this group were mainly caused by chronic mental disorders like schizophrenia and manodepressive psychosis. Tumours was the second category with 12.1 per cent of the total days followed by accidents (10.2 per cent) digestive disorders (9.9 per cent) and cardiovascular diseases (8.9 per cent). Respiratory diseases and infections formed 3.0 and 4.1 per cent respectively and musculo-skeletal diseases comprised 3.8 per cent of the total hospital days.

In the non-participant group 54 individuals had 1 737 hospital days for the three years, that is practically 11 days per individual and year. Alcohol psychosis and alcoholism accounted for 28.9 per cent of the total days in this group (Table 1).

The three new diagnostic categories (ARC, PAIC, NARC) gave a modified distribution (Table 2). The alcoholrelated conditions counted for 2 610 days, to compare with 2 330 days caused by alcohol psychosis and alcoholism. The excess number in the alcohol related conditions was due to the inclusion of the days caused by liver cirrhosis and pancreatitis. Thus the figures are practically the same.

The total 17 158 hospital days were grouped in the five screening GGT quintile classes and compared with the expected even distribution of GGT (Table 3). The observed days differed significantly in the lowest and

TABLE 1 HOSPITAL ADMISSIONS, TOTAL DAYS AND DAYS FOR ALCOHOLISM AND ALCOHOL PSYCHOSIS PER YEAR IN ATTENDANTS AND NON ATTENDANTS WITHIN THREE YEARS AFTER SCREENING

	Admission	Total days	Days for alcohol psychosis and alcoholism
Attendants participating in screening and hospitalized n = 963	0.7	5.9	0.8
Non attendants at random, hospitalized n = 54	1.2	10.7	3.1

*1)

*2)

* Calculated statistical significance between the groups (CHI² method on degree of freedom): 1) p < 0.05, 2) p < 0.001.

TABLE 2 TOTAL DAYS (NUMBER AND PER CENT) OF HOSPITALIZATION, FOR 963 MEN WITHIN THREE YEARS AFTER SCREENING IN DIFFERENT DIAGNOSTIC CATEGORIES

ICD groups (V excluded)	11 709	68.2
ICD group V*	5 449	31.8
	17 158	100.0
Non alcoholrelated conditions	12 142	70.8
Potentially alcoholinfluenced conditions	2 406	14.0
Alcoholrelated conditions	2 610	15.2
	17 158	100.0

* 2 330 days or 13.6 per cent of total days was caused by alcoholism or alcohol psychosis.

TABLE 3 RELATIVE PROBABILITY OF HOSPITALIZATION WITHIN THREE YEARS AFTER SCREENING IN QUINTILES OF GGT

	I	II	III	IV	V
Observed total days	1577	3383	2404	3984	5801
Expected total days	3430	3430	3430	3430	3430
Relative probability	0.46	0.99	0.70	1.16	1.69*

* Calculated statistical significance between the V: e quintile and the other groups (CHI² method four degrees of freedom) $p < 0.001$.

TABLE 4 NUMBER OF INDIVIDUALS IN PER CENT IN QUINTILES OF GGT AT SCREENING IN DIFFERENT DIAGNOSTIC GROUPS WITH HOSPITAL CARE

Diagnostic groups	I*	II	III	IV	V*	CHI ² four de- grees of freedom
Non alcoholrelated conditions n = 643	(7) 17	28	12	28	15 (8)	n.s.
Potential alcohol influenced condi- tions n = 193	(8) 15	16	13	17	39 (21)	$p < 0.001$
Alcoholrelated conditions n = 127	(2) 7	10	17	14	52 (43)	$p < 0.001$

* Figure within parenthesis shows the frequency in the lowest and highest decile respectively.

highest quintile. Thus the probability of hospitalization was 0.46 and 1.69 for the lowest and highest quintile respectively.

All admissions for the 963 men were analysed and grouped in the new categories. The ARC comprised 127 men, the PAIC 193 and the NARC had 643 individuals. The GGT values for the men in these groups were quintilized and compared with the screening GGT distribution (Table 4). There was a highly significant difference in the highest quintile (especially in the top decile) between the NARC group and the ARC group (15 against 52 per cent). In the PAIC group in the highest GGT quintile there was double the expected frequency (39 against 20 per cent).

The ARC group alone comprised 127 men or 13 per cent of the hospitalized men. Of the 963 men however, 175 had known manifest alcoholism and 58 of these men had admissions in non alcoholrelated conditions (Table 5). Another 21 men had admissions in the PAIC group. Thus totally 206 men or more than twenty (21.4) per cent of the hospitalized men had serious alcohol problems.

In the PAIC diagnostic category were included 193 or another 20 per cent of the 963 men. There is a wide variation in the influence of alcohol on the different conditions in this group. A man with several admissions within three years for conditions in different ICD groups e.g. fracture, hypertension and neuritis is highly suspected of having a drinking problem. On the other hand one single admission for gastritis should not cast suspicion on the individual even if cases hospitalized for gastritis are relatively strongly related to alcohol. Of the 193 men with potential alcoholinfluenced conditions one tenth ($n = 21$) had manifest alcoholism (Table 5) and in addition one fourth were highly suspected of having a drinking problem. Although the exact number can not be estimated, between one tenth to one half of all males in this group were judged to have at least some extent of drinking problems.

TABLE 5 INDIVIDUALS IN DIFFERENT DIAGNOSTIC CATEGORIES COMPARED TO THE ALCOHOLICS

	Nonalcoholrelated conditions	Potentially alcohol- influenced conditions	Alcoholrelated conditions
Total group n = 963	643	193	127
Alcoholics n = 175	58	21	96

DISCUSSION

This study was designed for the attempt to evaluate the influence of alcohol on the admissions to a general hospital and the reasons for the total hospitalization in middle-aged males. Earlier a similar classification of the admissions due to alcoholism and admissions possibly related to alcoholism has been reported (9). Lately thoracic fractures on routine chest X-rays have been used in screening for alcoholism (10).

In the present investigation 963 of 4 571 (21 per cent) apparently healthy men around 50 years of age consumed 17 158 hospital days within three years after screening. Chronic mental disorders comprised 18.1 per cent and tumours 12.1 per cent of the total days, but the vast majority of the days were classified as non-serious diseases. Although no economical calculation was intended it seems reasonable to argue that this high grade of hospitalization is not satisfactory and should probably, at least for financial reasons, not be continued. Alcohol psychoses and alcoholism accounted for 13.6 per cent of the hospital days in the attendants and 28.9 per cent of the days in the non-attendant group according to the ICD. These high figures are still more impressive, when taken into consideration that in total, a little less than thirty (29.2) per cent of the total hospital days were caused by the alcohol related and poten-

tially alcoholinfluenced illnesses altogether. This magnitude of the hospitalized alcohol related morbidity indicates the urgent necessity for "a public health strategy against alcoholism and its complications" (11).

GGT is one of the tests which have been most widely used in screening for alcoholism both in clinical and population studies (12-18). It has also been reported to be applicable in the control of heavy drinkers and alcoholics (6, 19, 20). We have already shown that 75 per cent of the men with GGT values in the top decentile of the GGT distribution can be classified as moderate to heavy drinkers (6, 15). In the preventive medical program in Malmö levels of GGT at screening were correlated to retrospective sickness cash benefit days (21). GGT values were also significantly increased in 46 per cent of those who died at follow up (7). In the present report 25 per cent of the men who were admitted to hospital had screening GGT values in the highest quintile of the GGT distribution. The frequency in the highest quintile was 2.5-3.5 times as high in the men with potentially alcoholinfluenced and alcohol related conditions as in the non-alcohol related group. The results illuminate the question of clinical significance by showing that in alcohol related conditions the risk of beeing hospitalized was seven times greater in men with GGT values in the highest quintile than in those with values in the lowest quintile. The same figure was two and a half times greater in the potentially alcoholinfluenced group but there was no difference in the men with the non-alcohol related conditions.

In nine hundred consecutive admissions to general medical wards 13 per cent of the patients were alcoholics (22) and in men at a surgical department almost one third had drinking problems (23). Of the total admissions in USA, 1975, 17.7 per cent were alcohol admissions among the males (24). In a health survey of 60-year old men, 12 per cent were registered for alcohol abuse (25). These 12 per cent consumed 40 per cent of the total hospital days of the whole cohort during the preceeding 10 years of life. Most studies have used drinking questionnaires. Although there are different admission policies in the developed countris' hospitals inpatients comprise a larger fraction of alcoholics than found in the general population (26).

Of 963 men in this study 127 or 13 per cent were judged to have drinking problems as they had been hospitalized for alcohol related conditions. An additional 79 individuals had been registered at the Department of Alcohol Diseases and been hospitalized for non-alcohol related or potentially alcoholinfluenced conditions. The latter group consisted of 193 men or another twenty per cent of the men (193/963). One tenth to one half of these men had at least some drinking problems. Thus about 25 per cent of the admitted middle-aged males were problem drinkers or alcoholics.

In the random subsample of non-attenders (Table 1), the overall morbidity was even more pronounced than in the attenders. It is well known that many medico-social complications related to alcohol are over-represented in screening non-participants (7), and this is supported in the present study by the higher frequency of hospital days for alcohol psychosis and alcoholism in this group. However, our main aim was a more detailed analysis of the responding part of the study population, with the screening investigation as a starting point and source of supplementary information including GGT. We believe that it is interesting and relevant that alcohol can be recognized as a factor of major importance for future ill-health even in this perspective of premature morbidity, short time after screening in apparently healthy middle-aged men. These observations warrant further investigation, particularly on the long-range findings, comparison with other risk factors and more extensive assessment of the non-attenders. These studies are under way.

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Alcohol consumption and premature death in middle-aged men

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Summary and conclusions

All the men living in Malmö born in 1926-9 were invited for a screening examination which included an assessment of alcohol consumption and measurement of gamma-glutamyltransferase (GGT) activity. They were followed for up to four years (median 2) and their mortality assessed. Sixty-two deaths occurred, 41 (0.9%) among the 4571 men who attended the screening investigation and 21 (1.3%) among the 1609 who did not respond to the invitation. Evidence of alcohol abuse or an alcohol-related cause of death was present in 25 (61%) of the deaths among the attenders and 13 (62%) of those among the non-responders. GGT values at the screening investigation were significantly increased in 19 (46%) of those who died, but established risk factors, such as cholesterol and triglyceride concentrations and blood pressure, had little predictive value.

Measurement of GGT provided an objective index of alcohol consumption, though the full clinical importance of a raised value needs further assessment. The finding that heavy alcohol consumption was the single most

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important factor associated with premature death in these middle-aged men has important implications for prevention.

Introduction

Though alcohol is recognised to be a major contributory factor in disease and premature death among middle-aged men, the medical profession still tends to underestimate the importance of alcohol in the range of disease.¹ There have been demands for a "public health strategy" to identify and prevent alcohol abuse through screening^{2,3} and for powerful political and economic measures to curb consumption. An important prerequisite for any of these measures is increased knowledge of the medical complications of alcohol consumption.

We established a screening clinic to try to identify and prevent alcohol abuse, and we report here a study on the short-term mortality of middle-aged men who were invited for screening.

Subjects and methods

Screening—A section of preventive medicine was established in autumn 1974 within the medical clinic at Malmö General Hospital. Total male birth-year cohorts in Malmö were invited to a screening investigation, where they underwent measurements of height and weight, pulse rate, blood pressure (standing and recumbent and before and after 10 minutes' rest), and skinfold thickness; simple pulmonary function tests; electrocardiography; and several fasting laboratory estimates, including γ -glutamyltransferase (GGT). All laboratory analyses were performed according to standard methods in the hospital's department of clinical chemistry. GGT was analysed according to the recommendation of the Scandinavian Enzyme Committee.⁴ The usual laboratory upper limit of normal for GGT was 1.0 μ kat/l, but in our screening clinic we used 1.44 μ kat/l as a cut-off limit for further investigation. Attenders were also asked to fill in a questionnaire on their alcohol intake. Findings at the screening investigation were checked one or two weeks later and if confirmed the patient was invited for further investigation and treatment at special outpatient clinics within the department of preventive medicine. These included clinics for blood pressure, lipids, "borderline diabetes," and raised GGT values.⁴

Study of population—Screening started in November 1974 with men born in 1926. Subsequent birth-year cohorts of men were examined consecutively in the following years together with women and a few younger birth-year cohorts. At the end of 1978 all men living in Malmö who were born in 1926-9 had been invited for screening—a total of

6180. Of these; 4571 (74%) responded. All the men were aged 48 or 49 years at the screening investigation, and they were followed-up for up to four years (median two years).

Mortality—Information on deaths occurring after the invitation to screening in these birth-year cohorts was obtained from a register at the department of pathology, Malmö General Hospital. This register covers all deaths in Malmö, including those where necropsy is not performed. There were 41 (0.9%) deaths among the 4571 men who attended for screening and 21 (1.3%) among the 1609 who did not. The necropsy rate was 90% (36/41) among attenders and 100% among the non-responders.

Alcohol consumption—To assess the part that alcohol consumption may have played in each death all accessible information on the deaths was reviewed: protocols from screening death certificates, necropsy reports, police reports, and hospital records, including those of the alcohol clinic of Malmö General Hospital. The men who died were classified as having an alcohol-positive history if this information showed at least one of the following: (a) a history of heavy alcohol consumption; (b) registration at the alcohol clinic; (c) a raised GGT value at the screening investigation which, after interview with one of us (HK), was considered to be due to heavy drinking.⁴ Those men who did not fulfill these criteria included a few who had only scanty or inconclusive information. All deaths from medical complications of alcoholism—for example, cirrhosis of the liver, oesophageal varices, and alcohol intoxication—and cases where alcohol intoxication contributed to the death according to necropsy reports were classified as probable alcohol-related deaths. Deaths from conditions that may have been related to alcohol consumption were classified as possible alcohol-related deaths.

Results

Table I shows causes of death, GGT values, and histories of alcohol consumption and smoking in the attenders at the screening clinic. Nineteen men had raised GGT activities and 21 a history of heavy alcohol consumption. These findings are related to the main causes of death in table II: raised GGT values and history of alcohol consumption were particularly prominent among men who committed suicide or died in accidents and those who died of miscellaneous causes (which included cirrhosis of the liver, bleeding oesophageal varices, etc).

Table III shows the causes of death according to the death certificates and a retrospective classification of alcohol consumption among non-responders. Mortality after the date of invitation to screening among non-responders was almost one and a half times that among attenders (1.3% compared with 0.9%). A directly alcohol-related cause of death was found in 10 of the 21 cases and a positive history of heavy alcohol consumption in 13 (62%).

There was a lower incidence of cardiovascular deaths, a higher

TABLE 1—Cause of death, alcohol and smoking history, and other findings at screening investigation in 41 participants who later died

Case No	Cause of death	GGT (μ kat/l)	History of heavy alcohol intake	History of smoking	Other screening findings*	Time between investigation and death (yr)	Alcohol-related death
1	Malignant glioma	0-42	—	+		1	
2	Cardiac hypertrophy, alcohol intoxication	1-93	+	+	BP (diastolic) 105 mm Hg	2	Probable
3	Alcohol and barbiturate intoxication	2-33	+	+		1 [†]	Probable
4	Malignant histiocytosis	2-98	+	+		1 [†]	Possible
5	Pancreas cancer	1-84	+	+		1	Possible
6	Alcohol intoxication	8-14	+	—	Triglyceride 2.8 mmol/l Triglyceride 3.5 mmol/l, relative body weight 1.4	1	Possible
7	Train accident (engine-driver)	2-42	+	—		1	Possible
8	Ethanol and hexapropylmate intoxication	0-82	+	+		1	Possible
9	Cor pulmonale	0-46	—	NA	PF 2.1 l/min, FVC 0.7 l	2 mth	Probable
10	Suicide (car exhaust)	0-60	—	+	Relative body weight 2.2	1 [‡]	Probable
11	Liver cirrhosis, chronic alcoholism	1-77	—	+	ESR > 100 mm in 1 h	2 [‡]	Probable
12	Bronchial cancer	1-44	—	NA		2 [‡]	Probable
13	Alcoholic cardiomyopathy	1-11	—	+	Hb 114 g/dl, glucose 8.6 mmol/l	2 [‡]	Probable
14	Pancreatitis	3-22	—	+		2	Probable
15	Diffuse abdominal adenocarcinoma	0-30	—	+		2	Probable
16	Pulmonary embolism	0-74	—	+		1 [‡]	Probable
17	Mycardial infarction	1-94	—	+	Hb 108 g/dl, ESR 89 mmol/l	1	Probable
18	Liver cirrhosis	31-7	+	+	Relative body weight 1.4, glucose 7.9 mmol/l	1	Probable
19	Mycardial fibrosis	0-91	+	+	Glucose 7.2 mmol/l	1	Probable
20	Pulmonary embolism	1-58	+	NA	BP 215/135 mm Hg	1 mth	Probable
21	Duodenal rupture (traumatic ?)	0-79	+	+		1	Probable
22	Dissecting aortic aneurysm	0-53	+	+		1	Probable
23	Mycardial infarction	1-86	+	+		3	Possible
24	Pancreatic neoplasm	0-47	+	+		3	Possible
25	Coronary sclerosis	0-35	+	+		3	Possible
26	Chronic myeloid leukaemia	5-15	—	—	WBC $59 \times 10^9/l$	3	
27	Cardiosclerosis, diabetes	1-93	?	NA	Triglyceride 3.1 mmol/l, glucose 7.3 mmol/l	3	
28	Malignant melanoma	0-84	—	+	BP 220/150 mm Hg, relative body weight 1.5; creatinine 438 μ mol/l	2	
29	Systemic hypertension	1-65	+	+		2	
30	Bronchial cancer	0-72	—	+		2 [‡]	
31	Pancreatic neoplasm	0-79	—	+	Relative body weight 1.4	2 [‡]	
32	Cardiosclerosis	0-75	—	+	BP 170/115 mm Hg	3	
33	Myelitis, myocarditis	0-33	—	—		3	
34	Cerebral haemorrhage	0-33	—	—	BP 190/115 mm Hg, relative body weight 1.6	2 [‡]	
35	Mycardial infarction	1-60	—	—	BP 155/110 mm Hg	2	
36	Cardiosclerosis	1-33	—	—		2	
37	Cardiosclerosis	2-59	—	—	BP 165/115 mm Hg	1 [‡]	
38	Bleeding oesophageal varices	0-56	+	+	BP 175/105 mm Hg, glucose 8.2 mmol/l	1 [‡]	Probable
39	Bronchopneumonia	2-96	+	+	Triglyceride 3.1 mmol/l, glucose 9.0 mmol/l	1 mth	Possible
40	Mycardial infarction	3-19	+	+	Operated angina pectoris 1966	1	
41	Mycardial infarction, diabetes	0-44	—	+	Known diabetes with complications	1	
		0-56	—	+		2	

* Recumbent blood pressure (BP) was measured after 10 minutes' rest. Relative body weight = actual weight/ideal weight for age, sex, and height. PF = Peak flow. FVC = Forced vital capacity. ESR = Erythrocyte sedimentation rate. Glucose value was that measured at 120 minutes during glucose tolerance test. WBC = White blood count.

Conversion: SI to traditional units—GGT: 1 μ kat/l $\approx$ 60 IU/l. Triglyceride: 1 mmol/l $\approx$ 89 mg/100 ml. Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

incidence of alcohol-related deaths, and a higher incidence of attendance at the alcoholic clinic among the non-responders than among those who attended the screening clinic (table IV). Nevertheless, over half the attenders had a history of heavy alcohol consumption and about half had raised GGT activities. Altogether 25 (61%) of the attenders had a history of alcohol consumption or raised GGT values, or both.

Table V shows that the premature deaths among attenders were

TABLE II—*Causes of death among participants and non-responders according to GGT activities and alcohol history*

	Participants			Non-responders		Total	
	No	No with raised GGT	No with history of heavy alcohol intake	No	No with history of heavy alcohol intake	No	No with history of heavy alcohol intake
Cardiovascular diseases	15	6	6	5	4	20	10
Cerebrovascular diseases	1	0	0	2	1	3	1
Miscellaneous causes ..	10	6	8	9	5	19	13
Malignant neoplasms ..	10	4	3	1	1	11	4
Suicide/accidents ..	5	3	4	4	2	9	6
Total ..	41	19	21	21	13	62	34

TABLE III—*Causes of death and history of alcohol consumption in non-responders*

Case No	Cause of death	Time between investigation and death (yr)	Alcohol history	Alcohol related death
1	Pulmonary embolism, pancreatitis	2 mnth	+	Probable
2	Pulmonary embolism	2	—	
3	Cardiac hypertrophy	1	+	Probable
4	Dissecting aortic aneurysm	1	—	
5	Myocardial infarction	1	+	
6	Myeloid leukaemia	1 mnth	—	
7	Burn injury, alcohol intoxication	1	+	Probable
8	Myocardial infarction	1 mnth	+	
9	Cerebral haemorrhage, diabetes mellitus	3	—	
10	Accidental drowning	2	—	
11	Pneumonia, myelopathy	2	—	
12	Hepatic cirrhosis	2	+	Probable
13	Colonic carcinoma	2	+	
14	Hepatic cirrhosis	2½	+	Probable
15	Respiratory insufficiency	2	—	
16	Suicide, depression	2	—	
17	Ventricular ulcer with haemorrhage	1	+	Probable
18	Subdural haematoma	1½	+	"
19	Myocardial fibrosis, alcohol intoxication	1	+	"
20	Drowning, alcohol intoxication	1	+	"
21	Oesophageal varices	1	+	"

TABLE IV—Comparison between attenders and non-responders. Results are numbers of subjects

	Participants	Non-responders	Total
Relative mortality	0.9% (1)	1.3% (145)	1%
Raised screening GGT (≥ 1.4)	19/41		
Known at alcohol clinic	11/41	9/21	20/62 (32%)
Alcoholic history	21/41	13/21	34/62 (55%)
Probable alcohol-related death	12/41	10/21	22/62 (36%)
Possible alcohol-related death	4/41		
Necropsy	36/41	21/21	57/62 (92%)

TABLE V—Numbers of deaths among participants according to GGT activities, serum cholesterol and triglyceride concentrations, recumbent diastolic blood pressure after 10 minutes' rest, and serum urate values. Quintiles are derived from distribution of values among all participants screened in 1926-9 birth-year cohorts ($n=4571$)

GGT ($\mu\text{kat/l}$)	≤ 0.4	-0.52	-0.67	-0.96	≥ 0.97
No of deaths	3	5	4	9	20
Cholesterol (mmol/l)	≤ 5.0	-5.5	-6.1	-6.8	≥ 6.9
No of deaths	12	11	7	5	6
Triglyceride (mmol/l)	≤ 1.0	-1.25	-1.50	-2.02	≥ 2.03
No of deaths	13	3	5	10	9
Diastolic blood pressure (mm Hg)	≤ 75	-85	-90	-95	≥ 96
No of deaths	6	12	10	2	11
Urate ($\mu\text{mol/l}$)	≤ 257	-292	-322	-358	≥ 359
No of deaths	5	8	3	10	15

concentrated in those whose GGT values were in the upper quintiles of the distribution of values among the whole population screened. A similar correlation did not exist for other values commonly regarded as risk factors (table V), though there was a slight tendency for those who died to have serum urate values in the upper quintiles; urate concentrations may also correlate with alcohol consumption.⁴

Discussion

In this unselected population of Swedish urban men alcohol was the most important single factor associated with death at about the age of 50: an alcohol-positive history was present in over half the men who died. Our study was a short-term prospective study of mortality in a fairly large population, uniform for age and sex, who were invited for screening and followed for up to four years (median two years). Our analysis of alcohol consumption was partly prospective and partly retrospective.

Many studies have confirmed the general impression that alcoholics have increased morbidity and mortality,^{1 2 5-8} and such features should also be identified in population studies.

Nevertheless, few population studies have been performed because of the difficulties of measuring alcohol consumption. Reliance on self-reported consumption in questionnaires makes findings open to doubt. At our screening investigation we used a modified Michigan alcoholism screening test,^{3,4} but we also used a biochemical index of heavy alcohol consumption.

With methods partly comparable to ours Tibblin studied 2992 men living in Gothenberg who were born in 1913.⁵⁻⁷ He found that of the 273 who died aged 35-55 17% were heavy drinkers or died from alcohol-related conditions.⁷ Lannerstad examined 49 deaths that occurred among 802 men in Malmö at the age of 55-60 years; in 27% he found signs of alcohol abuse, defined as registration at the alcohol clinic or a blood alcohol concentration at necropsy of more than 22 mmol/l, or both.⁸ The American epidemiological studies in Framingham and at Chicago Western Electric Company also showed an association between alcohol consumption and all causes of death,^{9,10} but comparisons are difficult because these populations were selected and the ages were different.

Serum GGT activity has been shown in series of alcoholics¹¹⁻¹³ and in population studies^{4,14-17} to be the best single biochemical index of high alcohol consumption. Nevertheless, the clinical significance of raised activities has still not been assessed. Measurement of GGT activity may play a useful part in screening investigations for alcohol abuse, especially in middle-aged men. We have already shown that 75% of those with raised GGT values can be classified as heavy users of alcohol.⁴ Our present results illuminate the question of clinical significance by showing that the risk of dying was six to seven times greater in men with GGT values in the highest quintile than in those with values in the lowest quintile. It remains to be seen whether the heavy consumer of alcohol with a normal serum GGT value on screening has a better outlook.

Interestingly, a high serum cholesterol value appeared to be an inverse risk factor for premature death—a finding supported by other reports.^{8,18} In a mortality study with a short follow-up such as ours some individuals may have already been ill and in poor nutritional state at the time of the examination, but the relationship between cholesterol concentration and premature death merits further consideration. It is hard to evaluate the role of smoking in our cohorts; 70% of the 41 attenders who died were smokers, and they were concentrated in the subgroup with a history of heavy alcohol consumption. This probably reflects the known association between alcohol consumption and smoking.

An assessment of drinking habits is a relevant aim in population investigations of middle-aged men, and measurements of

serum GGT may help if coupled with a clinical evaluation and treatment programme. Although our observations on short-term mortality permit no certain general epidemiological conclusions at this stage, we think that our findings are clear and relevant and carry important implications for prevention.

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IDENTIFICATION AND INTERVENTION OF HEAVY DRINKING
IN MIDDLE-AGED MEN
RESULTS AND FOLLOW-UP 24-72 MONTHS

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SUMMARY

During five years 8 859 of 11 643 (76.1 per cent) 46-49 year old men in Malmö participated in an intervention programme where serum gammaglutamyltransferase (GGT) was used in screening for heavy drinking. The study population consisted of 585 individuals born 1926-1933 with two consecutive GGT values in the upper decentile of the GGT distribution randomly allocated either to an intervention group or to a control group. The subjects in the intervention group (n = 317) were further investigated and 75 per cent of them were judged to have elevated GGT values caused by alcohol consumption. These individuals were repeatedly motivated to lower their overall alcohol consumption and monitoring GGT measurements were used as a biofeedback method in the treatment programme. The controls were informed by letter to be restrictive with their alcohol consumption and that they should receive new invitations for measurements of their liver enzymes after two, four and six years. The intervention and control groups were well matched and longterm followed-up. Two and four years after the screening investigation the GGT values, in both groups, were significantly decreased. Also the new individuals registered at the Department of Alcohol Diseases after the screening investigation were practically of the same number. There were differences, however, between the two groups with regards to sick absenteeism, hospitalization and mortality. A significant reduction was found in sick absence during four years by 80 per cent, in hospital days during five years by 60 per cent and in mortality during six years by 50 per cent in the intervention group, compared with the control group. Thus the intervention programme was effective in preventing medico-social consequences of heavy drinking.

INTRODUCTION

Long-term follow-up studies of treated and untreated alcoholics have revealed that over seven to ten years more than half of the alcoholics remit or die.^{1, 2, 3} These disheartening facts demonstrate the need for a strategy of early detection and treatment of drinking problems and alcoholism in the preclinical stages. To be defined as effective, treatment must change the projected natural course of the illness.⁴

Emrich found in his review⁵ that more treated than non-treated alcoholics improved, suggesting that formal treatment at least increases an alcoholics changes of reducing his drinking problem. There is no evidence, however, that a specific type of treatment makes a difference in outcome.^{4, 6}

In recent literature, various methods of behavioral treatment and control of problem drinking and alcoholism have been reported.^{7, 8} Treatment of heavy drinking has been thought to possibly prevent the development of overt alcoholism.⁹ Controlled social drinking is reported to be a relevant treatment goal in subgroups of alcoholics.^{10, 11}

In a continuing screening and intervention programme in Malmö we have been applying the same principles since 1974.¹² The aim has been to identify heavy drinkers among healthy middle-aged men and to intervene in their drinking habits and incipient drinking problems. The principles of open discussion and patient access to control measurements previously used for many years in the treatment of hypertension and hyperlipidaemia have been followed.

Serum- γ -glutamyltransferase (GGT) is one of the tests which has been most widely used in screening for alcoholism both in clinical and population studies.¹³⁻¹⁹ It has also been reported to be useful in monitoring heavy drinkers and alcoholics in small to moderately sized groups and over short observation periods.²⁰⁻²¹

We have reported that 75 per cent of those men with GGT values in the top decentile of the GGT distribution can be classified as moderate to heavy drinkers^{12, 22} and that it is feasible to influence their drinking habits. The aim is prevention of alcohol related disabilities and alcoholism on an individual basis.

This report further characterizes individuals in the top decentile of the GGT distribution according to the results of further treatment. Matched groups were selected for intervention or control. These groups have been followed and compared for a period of 24 to 60 months. The outcome has been analysed in terms of GGT levels, drop out frequency, morbidity and mortality.

STUDY POPULATION AND METHODS

Screening investigation

All male Malmö residents born 1926-1933 (n = 11 643) were invited to a planned screening programme at the Department of Preventive Medicine. From October 1974 to November 1979 records of total birth year cohorts were obtained from the population records and total cohorts were invited by letter to the medical investigation. The final attendance rate after two or three invitations was 76.1 per cent i.e. 8 859 men attended the screening. The aims were to attack the major middle-aged health risks related to cardiovascular disease, diabetes and heavy drinking.

The screening investigation included a large questionnaire, weight and height measurements, pulse and blood pressure registration, an oral glucose tolerance test and a number of other laboratory analyses. All variables were analysed by standard methods. The details of the screening have been given elsewhere.¹²

All investigations were performed in the morning after an overnight fast. During the oral glucose tolerance test the participants completed the questionnaire. This was comprised of a box system according to Collen²³ or a corresponding computer program²⁴, where each question was answered by "yes"-, "no"- or "don't know". Included in the questionnaire were nine questions about drinking habits.²⁵

Serum- γ -glutamyltransferase (GGT)

The main interest in this study of heavy drinking was to trace and identify individuals with incipient drinking problems. For this purpose the enzyme serum- γ -glutamyltransferase (GGT) was analysed consecutively in all males by standard methods.²⁶ The upper normal laboratory value was $< 1.08 \mu\text{kat/l}$. All men in the top decentile of the GGT distribution ($> 1.40 \mu\text{kat/l}$) were invited for repeated analysis.

Selection and randomization of the study population

Individuals with GGT values in the top decentile of the screening distribution were invited for a repeat analysis of the GGT value within three weeks. The reason for the second test was to ensure consistently elevated GGT values in the population selected. This study started as a pilot study and in the 1926 birth year cohort individuals with hypertension, hyperlipidaemia, diabetes mellitus and impaired glucose tolerance were excluded from the material. From the 1927 birth year cohort, however, only individuals with systemic hypertension and high GGT values were excluded by referral to the hypertension clinic. All others with high GGT values (except some cases with diabetes mellitus or pronounced hypercholesterolemia) were included in the material. In total 585 individuals or 6.6 per cent of the attendants were further investigated.

Intervention group

All individuals from the pilot study born in 1926 were included. In the other birth year cohorts half of the individuals with two consecutive high GGT values ($> 1.40 \mu\text{kat/l}$) were randomly allocated to the intervention group. Thus 261 men with even birthdate and uneven birthmonth or uneven birthdate and even birthmonth and an additional 56 men born in 1926 (total 317 subjects) were invited for further assessment at a special outpatient clinic at the Department of Preventive Medicine.

A general physical examination and liver tests were performed and a history was obtained during an interview designed to elicit a detailed

drinking history. The details of assessment of drinking habits and contacts with the individuals at the outpatient clinic have been given elsewhere.²²

All patients were offered continuing follow-up with consultations with the same physician every third month and monthly GGT tests and reinforcing contacts with the same nurse. Counselling was focused on living habits. A treatment goal of moderate drinking rather than abstinence was agreed upon. The individuals were considered to have their weaknesses and frequently exhibited slight contradictions in personal contact situations but this was not regarded as disease. The subjects were offered support and encouragement in their efforts to change drinking habits but were given full responsibility for the outcome of their participation. Moderate drinking was tolerated when necessary as long as GGT values did not rise. The subjects were carefully informed of the GGT level at every check-up and stimulated to attain normal levels. When the GGT value had stabilized at an acceptable level the frequency of therapeutic contacts was reduced.

Control group

The other half of the individuals with two consecutive high GGT values were allocated to the control group ($n = 268$). They had even birthdate and even birthmonth or uneven birthdate and uneven birthmonth.

Initially, 26 consecutive controls were referred to the medical clinic for detailed investigation including liver biopsy. After the investigation they were followed up at the Department of Preventive Medicine. The rest were informed by letter that they had an impaired liver test. They were told in the letter to live as usual, but to be restrictive with alcohol beverages, and that they would be invited for new liver tests after two years. Understandably, some of the individuals ($n = 56$), especially those with borderline abnormalities in some other test value such as serum-triglycerides, requested further investigation and treatment, and were therefore excluded from the control group. The remaining "reduced control group" consisting of 212 men received invitations by letter after

two, four and six years for a repeat GGT-test at the Department of Preventive Medicine.

The selection of the study population is summarized in Table I.

Table I. Study population. Controls "under treatment" are individuals assigned to the control group who were under treatment for borderline abnormalities.

	<u>N</u>	<u>Per cent</u>
Total cohort born 1926-1933	11 643	
Attendants participating in the screening	8 859	76.1
Attendants in upper decetile of GGT	796	9.0
Not attending control GGT	53	
Control GGT under cut off point	69	
Hyperlipidemia	35	
Hypertension	42	
Diabetes mellitus	12	
Remaining GGT material	585	6.6
Controls "under treatment"	56	
Reduced control group	212	
Controls (total)	268	
Intervention group	317	

Comparison of the intervention and control groups

As the two groups were collected during five years, calculations were performed to evaluate potential differences in test values at screening and the parameters measured during the follow up. From the questionnaire of 260 questions, 68 were selected and an additional 17 biochemical measurements were compared between the intervention (n = 261) and reduced control (n = 212) groups. Furthermore, the records were searched for all individuals in both groups who had been registered at the Department of Alcohol Diseases

from 1968 to the screening investigation. The total sick days per year were analysed for both groups during the 21 years prior to screening.

Statistical methods

For each of the 68 questions answered at the screening, the two groups were compared; in most cases an ordinary chi-square test was used but in 11 of the 68 questions we used Fisher's exact test instead because of the small number of affirmative answers to those questions. The two groups were tested by means of t-tests for differences in the quantitative background variables measured at the screening and also when these variables were compared during the follow-up.

RESULTS

Comparisons between the intervention group and reduced control group at the screening investigation _ _ _ _ _

The 261 men born 1927-1933 in the intervention group were compared with the 212 final controls. The frequency of affirmative answers to different questions in the screening questionnaire was compared and there was no significant difference between the two groups. Table II gives the frequency of affirmative answers to 30 questions concerning symptoms and treatment for hypertension, smoking and drinking habits, recent symptoms of diseases and several social parameters. Individuals in both groups had a remarkably high frequency of earlier disease symptoms and impaired social adjustment. Thus 20 per cent of the individuals in both groups reported high blood-pressure and about nine per cent used antihypertensive drugs. Present or earlier symptoms of back-pain were reported by 51 per cent, nervous symptoms by 19 per cent and hospitalization for psychiatric disorders by six per cent.

Thirty per cent of the men were presently under a doctor's control, 27 per cent had previously been married, 21 per cent had changed their place or type of employment during the last five years, 18 per cent had had sick

Table II. Affirmative answers to questions in per cent in the reduced control group and the intervention group at the screening investigation

	Intervention group (n = 261)	Control group (n = 212)
1. Have you ever been informed that you had high blood pressure?	23.0	17.8
2. Do you use medication for hypertension?	8.9	8.9
3. Do you smoke?	64.7	55.9
4. Do you smoke more than 20 cigarettes a day?	21.6	21.6
5. Are you a teetotaler?	3.7	6.1
6. Do you take a drink before going to a party?	20.4	21.1
7. Do you usually drink a bottle of wine or corresponding amounts of alcohol over the week-end?	38.7	41.3
8. Do you drink a couple of drinks (or beers) a day to relax?	18.2	17.4
9. Do you tolerate more alcohol now than you did ten years ago?	14.9	16.0
10. Have you difficulties not drinking more than your friends?	4.1	8.0
11. Do you fall asleep after moderate drinking without knowing how you got to bed?	7.8	10.3
12. Do you have a bad conscience after drinking?	13.0	15.5
13. Do you take a drink (a beer) the day after a party?	28.6	24.9
14. Do you try to avoid alcoholic beverages for a determined period of time e.g. a week?	29.7	30.5
15. Are you presently under a doctor's control?	29.0	31.0

	<u>Intervention group</u>	<u>Control group</u>
16. Have you been treated for tuberculosis of the lung?	2.6	5.2
17. Have you undergone an operation for an ulcer?	4.5	2.3
18. Have you had a kidney stone attack?	12.3	15.5
19. Have you had chronic back-pain?	53.2	49.3
20. Have you had gout?	0	1.9
21. Have you ever used sleeping pills regularly during a longer period?	14.9	13.6
22. Do you use sleeping pills more than three times a week?	8.2	7.0
23. Have you been treated for nervous symptoms?	17.5	20.7
24. Have you ever been hospitalized for a psychiatric disorder?	4.8	8.5
25. Have you previously been married?	28.6	25.4
26. Do you have sedantary work?	35.3	36.6
27. Do you have heavy physical work?	16.0	18.3
28. Have you changed your place or type of employment during the last five years?	18.6	23.9
29. Have you had sick leave at least three times during the last year?	18.2	18.3
30. Do you receive full disability pension?	3.3	3.3

The significance of the difference of the frequency of affirmative answers between the intervention and the reduced control group has been tested by means of ordinary chi-square test or by Fischer's exact test. Only one of the 68 tests showed any significant difference, namely the one testing gout (no.20). In the intervention group there was a significantly ($p < 0.05$) lower frequency of gout than in the control group.

leave at least three times during the last year and three per cent received full disability pension. Sixty per cent of the males were smokers and about 22 per cent smoked more than 20 cigarettes a day. Also the frequency of affirmative answers to the questions about drinking habits was generally twice that of the total population investigated.

The biochemical and physical measurements compared at screening were: length, weight, pulse, systolic and diastolic blood pressure (in recumbent position after 10 minutes rest), hemoglobin, hematocrit, uric acid, creatinine, cholesterol, triglycerides, GGT, ASAT, ALAT, fasting blood glucose and blood glucose at 120 minutes in oral glucose tolerance test. ALAT was the only test in which there was a statistically significant difference between the intervention and reduced control group. The mean ALAT value for the control group was 0.17 $\mu\text{kat/l}$ higher than that for the intervention group ($t = -2.63$). Non-significant differences were also found for ASAT and GGT with higher means by 0.08 and 0.29 $\mu\text{kat/l}$, respectively, in the control group. ($t = -1.28$ and -1.72).

The intervention group had an average total of 478 sick days per year during 1955-1975 compared with 437 days for the control group and the difference was not statistically significant ($t = 0.52$). Four years before the screening, however, the mean yearly sick absence was 43 days and 25 days respectively, in the same two groups and thus significantly different ($t = 2.63$). Two years before screening the difference was smaller, being 51 days versus 37 days ($t = 1.57$, n.s.).

Thirty-seven individuals from each group had been registered at the Department of Alcohol Diseases before the screening investigation.

Follow-up results

For the 56 individuals born in 1926 there was no control group so these individuals were analysed separately. Two dropped out before the intervention, the others have been followed at least six years and the results are summarized in Figure 1. Seven died and 23 were later dropouts. Of the 51 individuals who participated for a relatively long period, 22 men (43 per cent) improved their GGT levels and some of them radically changed their drinking habits (Table III).

Table III Results in 72 months follow up of 56 men born 1926

Follow up months	Drop outs		Dead	
	N	%	N	%
Dropped before interview	2	3.5	0	
0 - 12	9	16.0	0	
13 - 24	7	12.5	3	5.0
25 - 48	4	7.0	1	2.0
49 - 72	1	2.0	3	5.0
	23	41.0	7	12.5

Three of the deaths occurred in individuals which had earlier dropped out. The causes of deaths were Pancreas cancer, Pancreatitis, Alcohol intoxication, Myocardial infarction (2 cases), Subdural haematoma and Liver cirrhosis. Four cases were alcohol related deaths. Fiftyone were followed a longer period and 45% were unchanged, 43% improved and 12% impaired in their GGT levels.

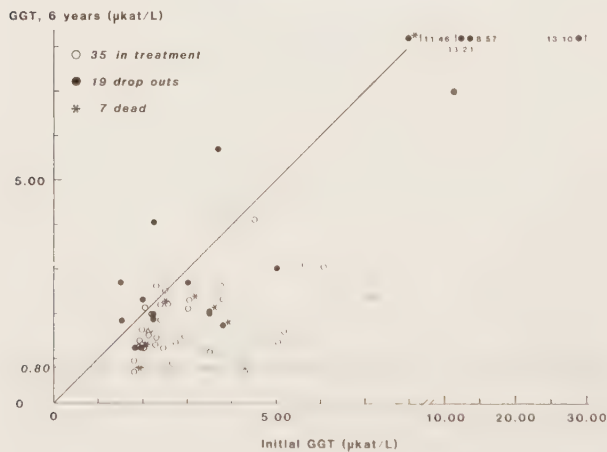


Figure 1. Follow up results during 72 months for 54 men born 1926.

The GGT levels in the males born 1927-1933 in the intervention group (n = 261) were compared with the 212 controls after two and four years participation. In the intervention group, values were the mean of all observations during the two and the four year periods. In the controls the initial GGT level was compared with a single observation at two and four years respectively. Comparisons were calculated within and between the groups. The results are given in Table IV.

Table IV Decreases in GGT levels from screening during two years and four years follow up in all cases in the intervention group remaining in treatment and all "reduced" controls who responded to the invitation for re-screening with GGT two and four years after initial test.

	Decrease from screening until two years follow-up	Decrease from screening until four years follow-up
Intervention group *	n = 153	n = 74
	m = 0.466	m = 0.735
	SD = 1.27	SD = 1.68
	P < 0.001	P < 0.001
Reduced controls **	n = 154	n = 88
	m = 0.450	m = 0.584
	SD = 2.20	SD = 1.36
	P < 0.01	P < 0.001

The differences between the intervention and control group were not statistically significant.

* In the intervention group the comparisons were calculated between the initial GGT and the mean of all values measured over the period.

** In the controls the comparisons were calculated between the initial GGT and a single test at 2 and 4 years respectively after screening.

The mean sick days per year two years and four years after entering the screening investigation were compared between the intervention and control group. The results are given in Table V. During the four years the mean sick days per individual and year increased from 24.0 to 29.3 days in the intervention group, or by totally 5.3 days. In the reduced control group the corresponding figures were: 24.7 to 51.9 days or totally by 27.2 days. The differences between the groups were statistically significant ($p < 0.05$), both at two and four years follow-up. The total difference between the groups after four years was 22 days per individual.

Table V Sick days per individual and year during four years before the screening investigation and at two and four years follow up for the intervention and reduced control groups *

	Sick days per individual and year		
	-4--0 years	0-2 years	2-4 years
Intervention group	24.0	28.2	29.3
	n = 163	n = 160	n = 90
Reduced control group	24.7	37.9	51.9
	n = 144	n = 138	n = 94
Significance	n.s.	$p < 0.05^Z$	$p < 0.05^Z$

^Z Mean of the differences for each individual in both groups calculated by t-test, i.e. 4.2 and 5.3 days in the intervention group compared with 13.2 and 27.2 days in the controls.

* Individuals who had more than totally 730 sick days i.e. half a year during all four years until the screening investigation were excluded. In the intervention group these numbered 17 and 4 in the controls.

Follow-up of hospitalization and alcohol related morbidity during
the five years after screening _ _ _ _ _

Data on diagnoses and duration of hospital inpatient care were collected and classified according to the International Classification of Diseases (ICD)²⁷ for the total study population. In this study all males born 1927-1931 were included and data for the five years after the screening investigation were available.

The intervention group contained 195 men in these birth year cohorts and 68 had been hospitalized. The reduced control group consisted of 180 males and 65 of them had admissions to hospital. In the total controls for these birth year cohorts the respective numbers were 219 and 81.

The reduced control group had 1 644 hospital days compared with 808 days for the men in the intervention group. The ratio was 2.2 and when the days were compared in different diagnostic categories the corresponding ratios were 3.2 in mental disorders, 1.3 in gastrointestinal disorders and 3.0 in accidents or injuries (Table VI). Comparison between the total control and the intervention groups gave more pronounced differences (Figure 2). Thus the ratio in total hospital days between the groups was 2.4. The ratios in mental disorders, gastrointestinal disorders and accidents or injuries were 4.1, 1.3 and 2.9 respectively.

In order to confirm the influence of alcohol on hospitalization the alcohol related conditions were grouped together. These conditions were alcohol psychosis (291.00-99), alcoholism (303.00-99), liver cirrhosis (571.00-99) and pancreatitis (577.00). In the reduced control group 20 men had 482 days compared with 13 individuals in the intervention group who consumed 133 hospital days. The ratio of total days was 3.9 (Table VII). The corresponding ratio for the total control group compared to the intervention group was 5.0 (Figure 3).

Table VI Hospitalization and morbidity during five years follow up in the reduced control group and the intervention group, men born 1927-1931

	Total hospital days *	Number of individuals	Days in diagnostic category			Accidents, injuries (XVII)
			Mental disorders (V)	Gastrointestinal disorders (IX)		
Reduced control group (n = 180)	1 644	65	465	198		247
Intervention group ** (n = 195)	808	68	155	163		89
Ratio	2.2	1.0	3.2	1.3		3.0

* The hospitalization was also calculated as the sum of the mean values for each individual who had been hospitalized in the reduced control and intervention group. In the former group there were 416.2 days compared with 209.7 days in the latter, ratio 2.1. Mean values in the diagnostic categories were: 151.7 (V), 38.4 (IX) and 62.1 (XVII) days compared with 43.2, 50.4 and 24.6 days respectively. The ratios were 3.5, 0.8 and 2.5.

** Of the total 808 hospital days in this group 27 days were caused by individuals who had been referred to the Department of Internal Medicine for special investigation because of unclear GGT values. Of the drop outs within six months 16 individuals had consumed 252 of the 808 hospital days.

Table VII Hospital days in alcohol related conditions (alcohol psychosis, alcoholism, liver cirrhosis and pancreatitis) at two-five years follow up in the reduced control group and the intervention group

	Total hospital days	Individuals
Reduced control group (n = 180)	482	20
Intervention group * (n = 195)	133	13
Ratio	3.9	1.7

* Of the 133 hospital days, none had been caused by individuals in the subgroup non alcoholic GGT.

A record of all individuals who were registered at the Department of Alcohol Diseases within six years after screening was also attained. In the intervention group there were nine new cases compared with ten in the controls. Seven of the nine men in the intervention group had 81 hospital days and 50 of these days were consumed in alcohol related conditions. For the ten controls the corresponding numbers were 546 days and 231 days respectively. The ratios between the controls and intervention group were 4.7 and 3.2 in total days and days in alcohol related conditions respectively.

Finally table VIII gives the causes and time of death within five years follow up. There were twice as many deaths in the control group than in the intervention group (10 versus 5) and the ratio of probably alcohol related deaths was also 2 (4 versus 2).

DISCUSSION

In the literature we have found few controlled studies on the treatment of problem drinkers.^{28, 29} The need for adequate study design including the use of control groups, validated measurement tools and simple statistical techniques³⁰ has been stressed.

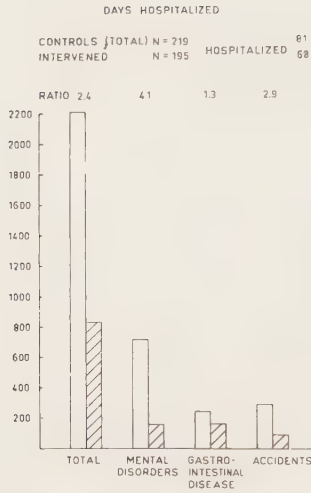


Figure 2. Hospitalization and morbidity in different ICD categories during five years follow-up in total control and intervention groups (men born 1927 - 1931).

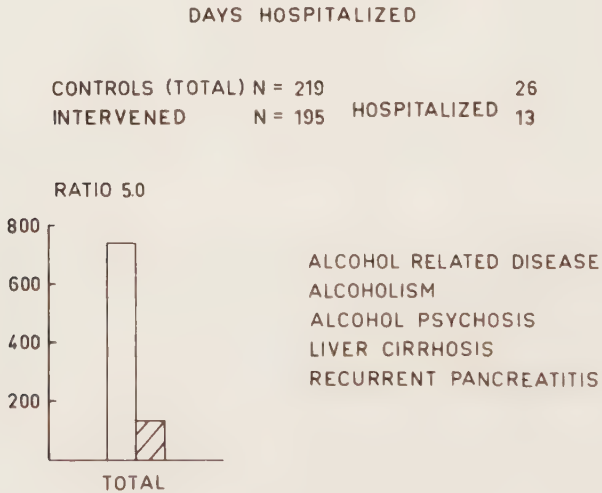


Figure 3. Hospital days in alcohol related diseases during five years follow-up in total control and intervention groups (men born 1927 - 1931).

Table VIII Cause and time of death within five years follow up in the intervention and the total control group

Case no	Cause of death	Time between screening and death (months)
I Intervention group (n = 261)		
1	Myocardial infarction	12
2	Alcohol and barbiturate intoxication	12
3	Liver cancer	22
4	Chronic alcoholism	47
5	Pancreas cancer	53
II Total control group (n = 269)		
1	Bronchopneumonia	8
2	Myocardial infarction	8
3	Myocardial fibrosis	9
4	Liver cirrhosis, chronic alcoholism	12
5	Liver cirrhosis, bronchopneumonia	21
6	Coronary sclerosis, chronic alcoholism	21
7	Myocardial infarction	25
8	Suicide (car exhaust)	39
9	Cerebral haemorrhage, myelofibrosis	43
10	Myocardial arrhythmia, chronic alcoholism	61

Case no 2 and 4 in the intervention group were primary drop outs, and the deaths were probably alcohol related deaths.

In the control group case no 4, 5, 6 and 10 were probably alcohol related deaths. Median time between screening and death was 21-22 months in both groups.

In this report 585 apparently healthy males, 46-49 years old at screening, with two consecutive elevated GGT values (mean $> 1.40 \mu\text{kat/l}$) in the top decentile of the GGT distribution were randomly allocated to either an intervention or a control group. In the intervention group an evaluation of drinking habits was performed and 75 per cent of the individuals could be classified as moderate or heavy drinkers.^{12, 22} The treatment consisted of counselling and discussion focused on drinking habits and reduction in alcohol consumption was agreed upon. The subjects were carefully informed of the GGT level at every check-up and stimulated to attain normal levels. The majority reported lowered alcohol consumption but this information was considered reliable only when it was accompanied by decrease in GGT level. Twentytwo per cent of the group dropped out within 24 months.

Screening for alcoholism and heavy drinking is at least a two-stage process GGT, which seems to be the most sensitive biochemical marker fails to detect two-thirds of heavy drinkers and alcoholics.^{25, 30} In the first step of detection the questionnaires (MAST), (CAGE) have a higher sensitivity and are more suitable.^{25, 31, 32} In the second step of identification of drinking problems, however, diagnostic aids and GGT in particular are most useful. Furthermore, in monitoring compliance, the measurement of GGT is a practicable and inexpensive tool. In focusing on the GGT value, which can be completely normalized when alcohol consumption is ceased, the patient perceives a direct advantage of restricting his drinking habits, which cannot be accomplished by the questionnaires. This bio-feedback technique is similar to the general principles of management (education, information and treatment) of patients with hypertension and diabetes mellitus. It is also in agreement with behaviour therapy techniques using positive reinforcement.^{7,8}

The intervention and reduced control groups were well matched at screening as seen in the frequency of affirmative answers to different questions at the screening investigation and in the laboratory test results. Thirty-seven individuals in both groups had been registered at the Department of Alcohol Diseases before the screening. The mean sick days per year four years prior to screening was higher in the intervention compared with the reduced control group.

After exclusion of the individuals, who had had sick leave more than half a year during all four years before the screening, the mean sick absenteeism was the same in both groups. The results at four years follow-up, showed a remarkable difference with a mean of 22 days per man more in the controls than in the intervention group. This high figure seems to be realistic, however, when considering the fact that individuals with elevated GGT levels had a high and rapidly increasing sick absenteeism even the years before the screening investigation.³³

Hospitalization and alcohol related morbidity were compared for the reduced control and intervention group during the five years after the screening. The ratios of 2.2 in total hospital days, 3.2 in mental disorders and 3.0 in accidents or injuries were found. When considering all alcohol related conditions the ratio was 3.9. In the comparisons between the total control group and the intervention group, the differences were still more pronounced. Thus the figures were 2.4 for total hospital days and 4.1 and 2.9 for mental disorders and accidents respectively. In alcohol related conditions the ratio was 5.0. Thus intervention resulted in drastic reduction in the need for hospitalization in this age group.

At follow up practically the same number of individuals from both groups had been registered at the Department of Alcohol Diseases but the extent of hospitalization was different. The controls had about four times as many hospital days as the men in the intervention group. Furthermore, the mortality was twice as great in the control group during the follow up period.

Our present results illustrate the possibility of a simple treatment programme to influence heavy drinkers to limit their drinking habits and possibly prevent alcoholism. Some of the individuals were totally abstinent for a period and continued drinking in a controlled way while some others could not limit their drinking and were lost. The majority of the men consciously reduced their consumption and adapted to a lower GGT level. The remarkable finding was that although the men did not cease drinking the counsellors' prolonged individual interest and support were

sufficient to preserve and maintain health and social adjustment for the majority of the cases. The major prerequisite of such a screening and intervention programme is not the diagnostic aids but rather access to patient and qualified professional manpower.

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